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SHRINKAGE AND CRACKING OF CEMENTIVE MATERIALS

Papers given and Discussion of them at the Symposium organised by the Road Building Materials Group of the Society of Chemical Industry in conjunction with the Ministry of Works. Held at the Royal Institution, London, May 8, 1946.

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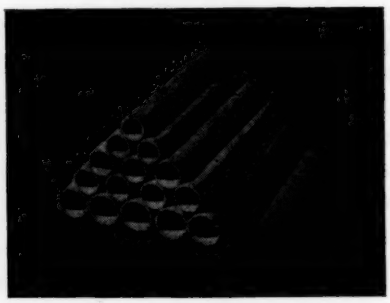

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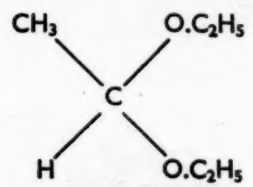

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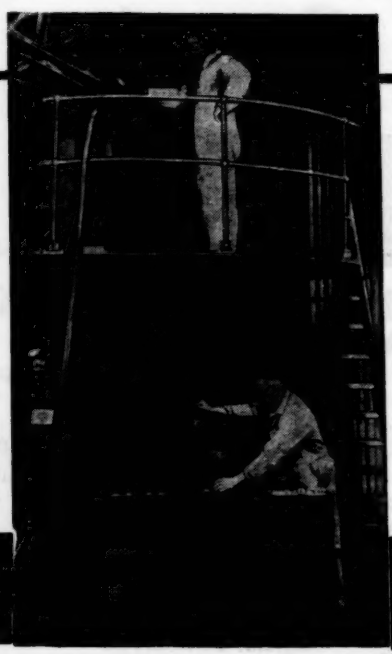

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NOTES.

Activating Influence of para-*Groups on the Lability of Chlorine in Chlorobenzenes.*

By G. M. Badger, J. W. Cook, and (Miss) Wendy P. Vidal.

In another investigation, the activating influence of the azo-group on a *p*-chloro-substituent towards reaction with an anionoid reagent (compare Borsche and Exss, *Ber.*, 1923, **56**, 2353) appeared to be somewhat greater than expected, and the present work was undertaken to obtain a quantitative measure of this effect. For this purpose, the percentage reaction with piperidine of various *p*-substituted chlorobenzenes has been determined, under standard conditions, by the gravimetric estimation of the halide ion in the reaction mixture, a method essentially the same as that used by Sandin and Liskear (*J. Amer. Chem. Soc.*, 1935, **57**, 1304). A preliminary trial of the method of Brewin and Turner (*J.*, 1928, 332), which involves weighing the piperidine salt which separates out on cooling the reaction mixture, gave much lower results than were obtained by the method of Sandin and Liskear. This was, no doubt, due to the uncertainty as to the composition of the precipitated salt (Powell and Dehn, *J. Amer. Chem. Soc.*, 1917, **39**, 1717), and also to the fact that piperidine hydrochloride is not completely insoluble in benzene.

Materials.—As solvent, sodium-dried, thiophen-free benzene, was used. Piperidine was dried over potassium hydroxide and kept over this reagent after being distilled. The *p*-chloronitrobenzene was a commercial sample, recrystallised from alcohol, m. p. 83°. *p*-Chloroaniline was also a commercial sample, recrystallised from benzene, m. p. 70°. *p*-Chloroazobenzene, prepared by the method of Jacobson and Loeb (*Ber.*, 1903, **36**, 4090) and recrystallised from alcohol, had m. p. 89°. *p*-Chlorobenzonitrile was prepared from *p*-chlorobenzamide by dehydration with phosphoric oxide; recrystallised from aqueous alcohol, it had m. p. 91°. Chlorobenzene was redistilled, b. p. 130°.

Method.—The *p*-substituted chlorobenzene (0·024 mol.) was heated under reflux in an all-glass apparatus, with piperidine (0·1 mol.) in anhydrous benzene (50 c.c.) for 8 hours. The aqueous extract, after being washed with a little benzene, was acidified with dilute nitric acid (5 c.c.) and the halide precipitated as silver chloride with 0·1N-silver nitrate. The precipitate was collected in a Gooch crucible and dried at 100°.

Results.—The following percentage reactions were obtained: *p*-chloronitrobenzene, 12·9, 12·9%; *p*-chlorobenzonitrile, 5·0%; *p*-chloroazobenzene, 1·97, 1·96%; chlorobenzene, 1·29, 1·31%; *p*-chloroaniline, 1·23, 1·24%.

The activating influence of the azo-group is, under these conditions, less than that of the cyano-group, and considerably less than that of the nitro-group. The amino-group exerts little effect.

One of us (G. M. B.) has been working with an Imperial Chemical Industries Research Fellowship.—University of Glasgow. [*Received, October, 24th*, 1946.]

An Improved Preparation of 1 : 8-*Dinitronaphthalene.*

By Herbert H. Hodgson and Edward R. Ward.

Whereas 1 : 8-dinitronaphthalene is scarcely attacked by aqueous sulphide even at 90° (Hodgson and Walker, *J.*, 1933, 1346; E.P. 392,914), it is rapidly converted in methanol suspension by a mixture of sodium sulphide and sodium hydrogen carbonate into sulphide dyes (Hodgson and Ward, *J.*, 1945, 794). When, however, the mixture of 1 : 5- and 1 : 8-dinitronaphthalene obtained by nitration of α-nitronaphthalene (Hodgson and Walker, *J.*, 1933, 721) is treated by the above sodium sulphide–sodium hydrogen carbonate mixture in methanol, in amount just sufficient to reduce the whole of the 1 : 5-dinitronaphthalene (about one-third, as determined by the complete removal of the 1 : 8-isomeride with sodium sulphite), the 1 : 8-dinitronaphthalene is entirely unattacked and remains behind after extraction with hydrochloric acid of the 5-nitro-1-naphthylamine mixed with it. Only one crystallisation of the residue from toluene is necessary for obtaining practically pure 1 : 8-dinitronaphthalene in almost quantitative amount.

The finely divided mixture (10 g.) of 1 : 5- and 1 : 8-dinitronaphthalene was suspended in boiling methanol (150 c.c.) and treated with the reducing agent (14 c.c.) [prepared by dissolution of crystalline sodium sulphide (24 g.) and sodium hydrogen carbonate (8 g.) in water (40 c.c.)] added in one batch, and the boiling was continued for 5 minutes; ice chips were then added quickly to the reddish-brown mixture before pouring it into water (total volume *ca.* 1 l.). No sulphide was present at the end of the reaction. The solid was filtered off, washed with water, and then extracted 4 times with boiling 8% hydrochloric acid (400 c.c. per time); the yield of extracted 5-nitro-1-naphthylamine was 8% of the original mixture and *ca.* 24% of the 1 : 5-dinitronaphthalene originally present. The acid-extracted residue, after being washed with water, was dried, and extracted twice with boiling toluene (200 c.c.); on concentration, the filtered toluene extract afforded 1 : 8-dinitronaphthalene (6·3 g., *i.e.*, 63% of the original mixture and *ca.* 95—96% of the amount of 1 : 8-dinitronaphthalene present; cf. the crude yield of *ca.* 40% obtained by Hodgson and Walker, *loc. cit.*), m. p. 169—171·5°. Increasing the amount of reducing agent beyond that used above lowered the yield of 1 : 8-dinitronaphthalene and also the purity of the 5-nitro-1-naphthylamine.

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals, and the Department of Scientific and Industrial Research for a Senior Research Award (to E. R. W.).
Technical College, Huddersfield. [*Received, October 25th*, 1946.]

OBITUARY NOTICE.

BEVAN LEAN.

1865—1947

BEVAN LEAN received his early education at Ackworth School, near Pontefract, and at Bootham School, York. He proceeded in 1887 to Owens College, Manchester, to study chemistry, where his exceptional ability was soon recognised. He held the Dalton Scholarship for research in 1891 and the Berkeley Fellowship in 1893, and was appointed to the staff of the Chemistry Department as Assistant Lecturer and Demonstrator in 1894. As a student he was resident at Dalton Hall, and was Tutor in Chemistry there from 1889 to 1894.

During these years at Manchester Lean was actively engaged in research, and was author or part author of six papers in the *Transactions* of the Chemical Society, published in the years 1892—1900. The first of these, with W. A. Bone, was on the " Behaviour of Ethylene on Explosion with less than its own Volume of Oxygen ", but the remainder showed that his chief interest lay in the realm of synthetical organic chemistry and dealt with butanetetracarboxylic acids, their homologues, and derived compounds. He took the external London Degrees of B.Sc. (1889) and D.Sc. (1894).

In 1897 Lean forsook an assured academic future to devote his life to school teaching. After four years as science master at Ackworth, he was appointed Headmaster of the Friends' school at Sidcot, Somerset, a position which he held for twenty-eight years. While there, he published with W. H. Perkin, Junr., in 1909 " An Introduction to Chemistry and Physics ". Lean was himself a lifelong member of the Society of Friends, and was deeply religious. Under his influence the school developed greatly, and the discipline of his scientific training and his whole-hearted devotion to the welfare of the school and the individual scholars combined to make him a headmaster of outstanding ability who won the respect and affection of many generations of Sidcot scholars. He leaves a widow and two sons. The elder, Oscar B. Lean, is in medical practice, and the younger, Owen B. Lean, is an entomologist with Imperial Chemical Industries Ltd.

W. BAKER.

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209. *Amidines. Part VII. Preparation of Amidines from Cyanides, Aluminium Chloride, and Ammonia or Amines.*

By P. OXLEY, M. W. PARTRIDGE, and W. F. SHORT.

Amidines and *N*-substituted amidines can be prepared from cyanides, aluminium chloride, and ammonia or an amine. The method gives good yields of *NN*-dialkylamidines, which are obtained in poor yield by the ammonium sulphonate method.

THE preparation of amidines from cyanides and ammonium or substituted ammonium sulphonates was described in Part I (Oxley and Short, *J.*, 1946, 147), in which the production of *NN*-disubstituted amidines was illustrated by a single example, namely *NN*-diphenylbenzamidine, obtained in 29% yield from phenyl cyanide and diphenylammonium benzenesulphonate. Application of the method to *p*-cyanophenyl methyl sulphone and piperidinium benzenesulphonate afforded NN-*pentamethylene*-p-*methylsulphonylbenzamidine* (27%), but our initial attempts to bring about a similar reaction with diethylammonium benzenesulphonate were unsuccessful. On raising the reaction temperature to 280°, however, *N*-ethyl-*p*-methylsulphonylbenzamidine was obtained in 0·8% yield, rising progressively to 4·5% at 325°. The same amidine was obtained from the cyanide and triethylammonium benzenesulphonate at 305° (0·2%), ethylammonium benzenesulphonate at 280° (41%), or ethylammonium chloride at 250°. (We find that it is essential to use the ammonium salt of a sulphonic acid or ammonium thiocyanate in order to obtain reasonable yields of unsubstituted amidines, but mono- and dialkylammonium chlorides may give good yields of substituted amidines.) Ammonium benzenesulphonate (81%) was obtained when diethylammonium benzenesulphonate and phenyl cyanide were heated at 350° and little cyanide was recovered. Similarly, piperidinium benzenesulphonate and phenyl or benzyl cyanide at 300° gave ammonium benzenesulphonate and benzamidinium or phenylacetamidinium benzenesulphonate. These dealkylations recall the progressive dealkylation of trialkylammonium chlorides on heating (Hofmann, *Proc. Roy. Soc.*,

1860, **10**, 595; Fileti and Piccini, *Ber.*, 1879, **12**, 1508) and Werner's observation (*J.*, 1914, **105**, 2769) that whereas ammonium methyl sulphate rearranges to methylammonium hydrogen sulphate and undergoes some demethylation above 240°, ammonium ethyl sulphate is completely decomposed on heating into ammonium hydrogen sulphate and ethylene. We ultimately found that a 7% yield of *NN*-diethyl-*p*-methylsulphonylbenzamidine could be obtained from the cyanide and diethylammonium benzenesulphonate at 224° and was identical with a specimen prepared by the Pinner method. *NN*-Diethylbenzamidine was prepared by the Pinner method and its *toluene*-p-*sulphonate* was almost completely decomposed at 215—250° into phenyl cyanide and diethylammonium toluene-*p*-sulphonate. These observations indicate that the sulphonate method is unlikely to be generally suitable for the preparation of *NN*-dialkylamidines.

The few cyanides which are known to combine directly with ammonia or amines to yield amidines contain polar groups which stimulate the additive capacity of the cyano-group (Part I, *loc. cit.*), and it seemed probable that the reactivity of cyanides could be stimulated, as is the case with carbonyl compounds, by combination with a catalyst having strong kationoid properties. A number of alkyl cyanide–aluminium chloride complexes have been described (Genvresse, *Bull. Soc. chim.*, 1888, **49**, 341; Perrier, *Compt. rend.*, 1895, **120**, 1424; *Bull. Soc. chim.*, 1895, **13**, 1031), and it seemed likely that catalysts of the Friedel–Crafts type might enhance the dipole condition of the molecule and with it its reactivity:

$$R{\cdot}CN + AlCl_3 \longrightarrow R{\cdot}C{\equiv}\overset{+}{N}{\rightarrow}\overset{-}{AlCl_3} \xrightarrow{NHXY} R{\cdot}C(NXY){:}\overset{+}{N}H{\rightarrow}\overset{-}{AlCl_3}$$

On the other hand, aluminium chloride and similar kationoid compounds readily yield ammines with ammonia and amines, so that the efficiency of the catalyst would be reduced by the presence of the competitive anionoid centre in the base and would also depend upon the solubility of the respective complexes in the reaction mixture. Thus, *p*-cyanophenyl methyl sulphone and aluminium chloride yielded an insoluble brown complex which gave only traces of amidine (Fuller reaction; *Nature*, 1944, **154**, 773) when heated with ammonia in various solvents, but *p*-methylsulphonylbenzamidine was obtained in 54% yield when the cyanide and aluminium chloride were heated with excess of molten urea, which acts as a source of ammonia and as a solvent. A number of amidines have been prepared by heating a cyanide and aluminium chloride with a base, and the scope of the method is illustrated by the examples in the Table. It will be noted that the method affords good yields of *NN*-dialkylamidines and is therefore a useful supplement to the ammonium sulphonate method.

Amidine (*a*).	Yield, %.	Amidine (*a*).	Yield, %.
Benzamidine (*b*)	57	N-2-*Pyridyl*-p-*methylsulphonylbenzamidine*	73·5
o-Nitrobenzamidine (*c*)	13	N-cyclo*Hexylphenylacetamidine*	90
p-Nitrobenzamidine (*c*)	60	*N*-*cyclo*Hexyl-1-amidino-*n*-heptane	98
p-Methylsulphonylbenzamidine (*c*)	54	1 : 3-*Bis*-(N-*phenyl*-4-*amidinophenoxy*)-*propane*	69
β-Naphthamidine (*c*)	3·8	*NN*-Pentamethylenebenzamidine	37
N-Phenylacetamidine (*d*)	50·5	*N*-Phenyl-*N*-methylbenzamidine	*ca.* 100
N-*cyclo*Hexyldiethylacetamidine	28	*NN*-Diethyl-*p*-methylsulphonylbenzamidine	*ca.* 100
N-Benzylbenzamidine	63	NN-*Pentamethylene*-p-*methylsulphonylbenzamidine*	98
N-*o*-Nitrophenylbenzamidine	15	NN-*Diphenylpicolinamidine*	76
N-2-*Pyridylbenzamidine*	62		
N-*Benzylanisamidine*	82·5		
N-cyclo*Hexylanisamidine*	94		
N-Phenyl-2 : 4-dichlorobenzamidine	74		

(*a*) The product was isolated as base, hydrochloride, picrate, or benzenesulphonate (see experimental section): the yields recorded refer to the pure compound first isolated and are based on the cyanide employed.
(*b*) Gaseous ammonia used.
(*c*) Urea (16 mols.) employed as source of ammonia.
(*d*) *NN'*-Diphenylacetamidine (3·9%) was also formed.

We have made a cursory examination of the use of other catalysts for the production of amidines since it might be desirable to avoid the use of aluminium chloride in certain cases. Several catalysts used in reactions of the Friedel–Crafts type, such as ferric chloride, zinc, chloride, and stannic chloride, have been found to promote the formation of amidines, and other compounds exhibiting kationoid activity were also effective (see Table below). Boron trifluoride failed to promote the union of benzyl cyanide and *cyclo*hexylamine at 140°; this may be due to the stability of monoamminoboron trifluoride.

Catalyst.	Amidine.	Yield, %.
Ferric chloride	*p*-Nitrobenzamidine (*a*)	30
Zinc chloride	Phenylacetamidine (*a*)	33
	p-Nitrobenzamidine (*a*)	38
	N-Phenylbenzamidine	31
	*N-cyclo*Hexylphenylacetamidine	6
Stannic chloride	*p*-Nitrobenzamidine (*a*)	56
Triphenyltin chloride	*p*-Methylsulphonylbenzamidine	74
Triphenylaluminium	*NN*-Pentamethylene-*p*-methylsulphonylbenzamidine	32
Aluminium *iso*propoxide	*p*-Methylsulphonylbenzamidine	Trace
Triphenyl borate	Benzamidine	60
	NN-Pentamethylene-*p*-methylsulphonylbenzamidine	3·5
	p-Methylsulphonylbenzamidine (*b*)	60

(*a*) Urea used as source of ammonia. (*b*) Tribenzyl borate was ineffective.

Experimental.

Cyanides and Substituted Ammonium Benzenesulphonates.

Benzamidine.—Phenyl cyanide (10 g.) and piperidinium benzenesulphonate (25 g.; 1·06 mols.) were heated at 300° for 14 hours and afforded benzamidinium benzenesulphonate, m. p. and mixed m. p. 175—175·5° (5 g., 18·5%), and ammonium benzenesulphonate, m. p. and mixed m. p. 283—285° (6·2 g., 36·5%).

Phenylacetamidine.—Benzyl cyanide (10 g.) and piperidinium benzenesulphonate (12·5 g.; 1 mol.) similarly gave phenylacetamidinium benzenesulphonate, m. p. and mixed m. p. 186—186·5° (2·4 g., 16%), and ammonium benzenesulphonate, m. p. and mixed m. p. 283—285° (2·7 g., 30%), after 14 hours at 300°.

N-*Ethyl*-p-*methylsulphonylbenzamidine.*—(*a*) A mixture of *p*-methylsulphonylphenyl cyanide(9·05 g.) and ethylammonium benzenesulphonate (10·15 g.; 1 mol.) was heated at 275—280° for 80 minutes and the residue was recrystallised from hot water (100 c.c.), giving recovered cyanide (2 g.), m. p. and mixed m. p. 140—141°. The aqueous solution was extracted with chloroform and made alkaline with 5N-sodium hydroxide, and the amidine (4·6 g.; 41%) was collected in chloroform. This amidine was obtained as a gum, but N-*ethyl*-p-*methylsulphonylbenzamidinium picrate* had m. p. 155·5—156° (Found: N, 15·4. $C_{16}H_{17}O_9N_5S$ requires N, 15·4%). The *toluene*-p-*sulphonate* had m. p. 242° (Found: C, 51·2; H, 5·6; N, 7·2; S, 15·9. $C_{17}H_{22}O_5N_2S_2$ requires C, 51·25; H, 5·5; N, 7·0; S, 16·1%).

(*b*) A mixture of the cyanide (5 g.) and ethylammonium chloride (5 g.; 2·2 mols.) was heated at 250° for an hour and afforded 1·3 g. of recovered cyanide and 3·5 g. (56%) of crude amidine which gave 3·7 g. (34%) of pure toluene-*p*-sulphonate, m. p. and mixed m. p. 242°. After 3½ hours at 224° a mixture of the cyanide (5·43 g.) and ethylammonium chloride (9·8 g.; 4 mols.) afforded 27·6% of recovered cyanide and 43% of amidine, isolated as toluene-*p*-sulphonate. The following experiments with 5·43 g. of cyanide and 2·45 g. (1 mol.) of ethylammonium chloride illustrate the influence of experimental conditions on the yield of amidine.

Temp.	200—202°	224°	224°	224°	230°
Time, hrs.	1	2	4	14	1
Recovered cyanide, %	92	51·6	44·2	38·7	64·5
Yield of amidine, % *	2·85	15·9	26·7	32·3	17·9

* Isolated as toluene-*p*-sulphonate, m. p. 242°.

(*c*) *N*-Ethyl-*p*-methylsulphonylbenzamidine was also produced when the cyanide (5·5 g.) and diethylammonium benzenesulphonate (7 g.; 1 mol.) were heated at temperatures within the range 280—326°. The reaction mixture was worked up as described in (*a*), and the principal basic product was identified by the analysis and mixed m. p. of its toluene-*p*-sulphonate. Before purification this salt gave a faint Fuller reaction and therefore probably contained traces of *p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate. The mother liquors may have contained *NN*-diethyl-*p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate as a minor constituent. The results are summarised in the following table.

Temp.	280°	295°	310—312°	325—326°
Time, hrs.	2	½	½	½
Recovered cyanide, %	85	82	71	42
N-Ethyl-*p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate (m. p. 242°), %	0·83	1·65	3·6	4·55

(*d*) Triethylammonium benzenesulphonate, prepared from its constituents and crystallised from *iso*propanol to constant m. p., formed hexagonal plates, m. p. 119° (Found: N, 5·5. Calc. for $C_{12}H_{21}O_3NS$: N, 5·4%). Norton and Westenhoff (*Amer. Chem. J.*, 1888, **10**, 133) record m. p. 120—121°. A mixture of this salt (12·95 g.; 1 mol.) and *p*-methylsulphonylphenyl cyanide (9·05 g.) was heated at 305—306° for 30 minutes. Gas evolution began at *ca.* 240° and continued throughout, the odour first resembling that of ethylamine but subsequently changing to that of a heterocyclic base. The product, which solidified on cooling, afforded 6·3 g. (70%) of recovered cyanide, m. p. 141—142°, and 0·55 g. of a crude base, from which only 0·04 g. (0·2%) of *N*-ethyl-*p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate, m. p. and mixed m. p. 242°, was obtained.

N-*Methyl*-p-*nitrobenzamidine.*—A mixture of *p*-nitrophenyl cyanide (7·4 g.) and methylammonium chloride (3·9 g.; 1·2 mols.) became homogeneous after an hour's heating at 224° and after a further

3 hours at this temperature afforded 4·3 g. of recovered cyanide, m. p. 147°, and 0·7 g. (8%) of N-*methyl*-p-*nitrobenzamidine*, m. p. 137·5° (Found: N, 23·4. $C_8H_9O_2N_3$ requires N, 23·5%). The *picrate* crystallised from *iso*propanol in needles, m. p. 174·5° (Found: N, 20·6. $C_{14}H_{12}O_9N_6$ requires N, 20·6%).

NN-*Diethylbenzamidine*.—Benziminoethyl ether (10 g.; b. p. 106—108°/16 mm., Wheeler, Walden, and Metcalf, *Amer. Chem. J.*, 1898, **20**, 71), diethylammonium benzenesulphonate (15·5 g.; 1 mol.), and anhydrous ethanol (20 c.c.) were kept at 50° for 21 hours, then cooled and filtered to recover diethylammonium benzenesulphonate (6·5 g.). The filtrate was evaporated under diminished pressure and the residue was shaken with 2N-sodium hydroxide and chloroform. The dried chloroform solution was evaporated and the residue distilled. The first fraction, b. p. 65—85°/3 mm. (1 g.), smelled of phenyl cyanide, and the amidine, b. p. 85—90° (almost entirely at 88—89°/3 mm.) (6·1 g., 51·6%), then distilled leaving a residue (1·5 g.) of 2 : 4 : 6-triphenyl-1 : 3 : 5-triazine, m. p. 236° (Found: C, 81·5; H, 5·1; N, 13·6. Calc. for $C_{21}H_{15}N_3$: C, 81·55; H, 4·9; N, 13·6%). Robin (*Ann. Chim.*, 1921, **16**, 113) records m. p. 235°. NN-*Diethylbenzamidinium picrate* crystallised from methanol in plates, m. p. 161° (Found: N, 17·35. $C_{17}H_{19}O_7N_5$ requires N, 17·3%), and the *toluene*-p-*sulphonate* had m. p. 126° (Found: N, 8·1. $C_{18}H_{24}O_3N_2S$ requires N, 8·05%). When the imino-ether, benzenesulphonate, and ethanol were refluxed for 14 hours (internal temperature 90°), the yield of amidine was 5·1 g. (43%).

NN-Diethylbenzamidinium toluene-*p*-sulphonate began to decompose with evolution of phenyl cyanide at 215—220°, and after ½ hour at 250° the residue afforded diethylammonium toluene-*p*-sulphonate, m. p. and mixed m. p. 103°, after being washed with ether and crystallised from *iso*propanol–ether (Found: N, 5·7. Calc. for $C_{11}H_{19}O_3NS$: N, 5·7%). Norton and Otten (*Amer. Chem. J.*, 1888, **10**, 140) record m. p. 88°.

Considerable pressure was developed when phenyl cyanide (8·5 g.) and diethylammonium benzenesulphonate (19 g.; 1 mol.) were heated in a sealed tube for 22 hours at 345—350°. The resulting mixture of brown oil and colourless plates was triturated with chloroform and gave ammonium benzenesulphonate, m. p. and mixed m. p. 283—285° (11·6 g., 81%). The oil isolated from the chloroform solution distilled over a very wide range and afforded neither fractions of constant boiling point nor crystalline picrates.

NN-*Diethyl*-p-*methylsulphonylbenzamidine*.—(*a*) A solution of *p*-methylsulphonylphenyl cyanide (9·05 g.) in ethanol (2·5 g.; 1·1 mols.) and chloroform (60 c.c.) was treated with a current of hydrogen chloride until 2·3 g. (1·3 mols.) had been absorbed. The imino-ether hydrochloride (8·4 g.), m. p. 220—225° (decomp.), was collected after being kept for 60 hours at room temperature (cf. Fuller, Tonkin, and Walker, *J.*, 1945, 636; Andrewes, King, and Walker, *Proc. Roy. Soc.*, 1946, *B*, **133**, 46). The imino-ether (5·6 g., 49%), obtained as a viscous gum by shaking the hydrochloride with 5N-sodium hydroxide and chloroform, was heated with diethylammonium benzenesulphonate (6 g.; 1·05 mols.) for 1½ hours at 140°. Alcohol was evolved, and trituration of the crystalline product with chloroform afforded an almost insoluble solid (0·35 g.) which separated from pyridine in colourless needles, m. p. >360°, and was probably 2 : 4 : 6-*tris*-p-*methylsulphonylphenyl*-1 : 3 : 5-*triazine* (Found: N, 8·0. $C_{24}H_{21}O_6N_3S_3$ requires N, 7·7%). Concentration of the chloroform solution afforded recovered cyanide (1·3 g., m. p. and mixed m. p. 141°) and then the crude amidine (2 g., 32%) which gave a picrate, m. p. 184·5°, identical with that obtained from *NN*-diethyl-*p*-methylsulphonylbenzamidine prepared by the aluminium chloride method (below).

(*b*) The cyanide (4·5 g.) and diethylammonium benzenesulphonate (23·1 g.; 4 mols.), heated at 224° for 14½ hours, afforded 3·5 g. of recovered cyanide and the crude amidine (0·5 g., 8%) which afforded the pure picrate, m. p. and mixed m. p. 184·5° (0·83 g., 7%). Almost the same yields were obtained when diethylammonium chloride (11 g.; 4 mols.) was used in place of the benzenesulphonate and the mixture heated at 224° for 2¼ hours.

(*c*) The preparation of this amidine by the aluminium chloride method is described below.

NN-*Pentamethylene*-p-*methylsulphonylbenzamidine*.—*p*-Methylsulphonylphenyl cyanide (4·5 g.) and piperidinium benzenesulphonate (24·3 g.; 4 mols.) were heated at 230° for 4 hours and gave 2·4 g. of recovered cyanide and 1·8 g. (27%) of *NN*-pentamethylene-*p*-methylsulphonylbenzamidine, m. p. 97°. The amidine afforded a toluene-*p*-sulphonate, m. p. 230—231°, and there was no depression in m. p. on admixture of the amidine and its salt with preparations made by the aluminium chloride method (see below).

*Preparation of Amidines from Cyanides, Bases, and Kationoid Reagents.**

Except where otherwise indicated, the cyanide and the base were employed in the proportion of one mol. of base per cyano-group, and one mol. of aluminium chloride (reckoned as $AlCl_3$) or of zinc chloride was added to the mixture. The experimental conditions used varied considerably and did not appear to be critical. The yields recorded are not necessarily the highest obtainable since a systematic examination of the effect of conditions on the yield of amidine was made in only a few cases. The reaction product, consisting of a complex of the amidine with the catalyst, was carefully decomposed with water and, when the amidine hydrochloride was sparingly soluble in water, it separated on cooling from the hot, filtered solution. Usually, however, the amidine was liberated from the solution by excess of aqueous sodium hydroxide, collected in chloroform, and then isolated as base, picrate, or hydrochloride. The methods employed follow closely those described in previous parts of this series, to which reference is made for earlier descriptions of many of the amidines (Part I, Oxley and Short, *J.*, 1946, 147; Part II, Oxley, Robson, Partridge, and Short, *ibid.*, p. 763; Part III, Oxley and Short, this vol., p. 382; Part IV, Partridge and Short, *ibid.*, p. 390; Part V, Hullin, Miller, and Short, *ibid.*, p. 394).

Benzamidine.—(*a*) A mixture of phenyl cyanide (2·1 g.) and aluminium chloride (5·3 g.; 2 mols.) was heated at 100° for 30 minutes in an atmosphere of dry ammonia, and the amidine was isolated as picrate, m. p. and mixed m. p. 239—240°. Yield, 3·95 g.

(*b*) Phenyl cyanide (2·06 g.), ammonium benzenesulphonate (3·5 g.; 1 mol.), and triphenyl borate

* See also B.P. Applns. 22748 and 22749 (4.9.1945).

(5·8 g.; 1 mol.) gave a 60% yield of benzamidinium benzenesulphonate, m. p. and mixed m. p. 175—175·5°, when heated at 160° in a stream of dry ammonia for 5 hours.

o-*Nitrobenzamidine.*—*o*-Nitrophenyl cyanide (5·6 g.), aluminium chloride (5 g.), and urea (36 g.; 16 mols.) were heated at 180° for 2 hours with vigorous stirring. The amidine was isolated as picrate, m. p. 228—229° (Found: N, 21·4. Calc. for $C_{13}H_{10}O_9N_6$: N, 21·3%). Yield, 1·9 g. The m. p. of *o*-nitrobenzamidinium picrate is recorded in Part I as 232—233° (decomp.).

p-*Nitrobenzamidine.*—(*a*) This amidine was prepared from *p*-nitrophenyl cyanide (1·5 g.), aluminium chloride, and urea in the proportions used in the previous example, and was isolated either as base, m. p. 216° (decomp.), or as picrate, m. p. 239—240° (Part I). After 15 minutes at 180° the yield was 26% and rose to 60% after 30 minutes. When only 8 mols. of urea were employed, the reaction mixtures solidified after 20 minutes and the yield of *p*-nitrobenzamidine was only 4%.

(*b*) A mixture of *p*-nitrophenyl cyanide (1·5 g.), urea (9·6 g.; 16 mols.), and zinc chloride (1·4 g.) afforded a homogeneous mixture after being stirred at 180° for 15 minutes, and after another 15 minutes at this temperature the yield of amidine, m. p. 212°, was 38%.

(*c*) A 9·1% yield of amidine was obtained when the cyanide (3 g.) and zinc chloride (2·8 g.) were heated at 180° for 15 minutes in a stream of ammonia. After 15 minutes at 135—140° the yield was 1·5%.

(*d*) When *p*-nitrophenyl cyanide (1·5 g.), urea (9·6 g.; 16 mols.), and anhydrous ferric chloride (1·6 g.) were heated to 120°, an exothermic reaction raised the temperature to 180°, and the cooled reaction mixture then afforded a 30% yield of the amidine.

(*e*) The cyanide (1·5 g.), urea (2·4 g.; 4 mols.), and stannic chloride (2·6 g.) afforded a 56% yield of amidine, isolated as picrate, m. p. 230—232°, after 30 minutes at 180°. Recrystallisation from methanol raised the m. p. of the picrate to 238—239°.

p-*Methylsulphonylbenzamidine.*—(*a*) A mixture of *p*-methylsulphonylphenyl cyanide (9 g.), aluminium chloride (6·7 g.), and urea (48 g.; 16 mols.) was heated at 180° for 30 minutes. The amidine was isolated as the picrate, m. p. and mixed m. p. 263—264° (Part IV). Yield, 11·5 g.

p-Methylsulphonylphenyl cyanide (4·5 g.) and aluminium chloride (3·3 g.; 1 mol.) afforded a brown complex when heated in benzene (250 c.c.). This solid, which softened at 95—105° and decomposed at 120—125° with gas evolution, gave a trace of amidine (Fuller reaction) when heated in a stream of ammonia in various solvents. A similar result was obtained when zinc chloride, ferric chloride, or stannic chloride was substituted for aluminium chloride. Only traces of amidine were formed when the cyanide and aluminium *iso*propoxide were heated in ammonia at 100° or 110°, 99% of the cyanide being recovered.

(*b*) A mixture of *p*-methylsulphonylphenyl cyanide (1·81 g.) and triphenyltin chloride (3·85 g.; 1 mol.; Kozeschkov, Nadj, and Alexandrov, *Ber.*, 1934, **67**, 1348) was heated for 24 hours at 100° in a stream of ammonia, and the amidine was isolated as p-*methylsulphonylbenzamidinium toluene*-p-*sulphonate*, m. p. 292—293° (Found: N, 7·6. $C_{15}H_{18}O_5N_2S_2$ requires N, 7·6%). The yield was 2·75 g. (74%).

(*c*) A 40% yield of the toluene-*p*-sulphonate was similarly prepared from the product obtained by heating the cyanide (3·62 g.) and triphenyl borate (5·8 g.; 1 mol.) in a stream of ammonia for 17 hours at 100°. No amidine was obtained when tribenzyl borate (1 mol.) was used in place of triphenyl borate.

β-Naphthamidine.—A mixture of β-naphthyl cyanide (1·5 g.), urea (9·6 g.; 16 mols.), and aluminium chloride (1·3 g.) evolved ammonia when heated but was not completely homogeneous after 1 hour at 180°. The product afforded β-naphthamidinium picrate (0·15 g.), m. p. 248°, and recrystallisation from methanol gave the pure product, m. p. and mixed m. p. 252° (Part I).

Phenylacetamidine.—Phenylacetamidinium picrate (1·18 g.), m. p. and mixed m. p. 227—228° (decomp.), was prepared from the homogeneous melt obtained by heating benzyl cyanide (1·2 g.), urea (9·6 g.; 16 mols.), and zinc chloride (1·4 g.) at 180° for an hour. The same m. p. is recorded in Part IV.

N-*Phenyl- and* NN′-*Diphenyl-acetamidine.*—Powdered aluminium chloride (66·6 g.) was added in portions during ¾ hour to methyl cyanide (20·5 g.) and aniline (46·5 g.) so that the temperature remained at 90—100°, and the mixture was kept at 100° for an hour. The mixture of bases (58·7 g.), isolated from the product in the usual way, afforded crystals (3·9%) of *NN′*-diphenylacetamidine, m. p. 131—132°, on recrystallisation from aqueous methanol. A second recrystallisation from aqueous methanol afforded the pure amidine, m. p. 133·5—134° (cf. Part III). The original mother liquor was made acid to brilliant-yellow with ethanolic picric acid and the crude picrate was recrystallised from methanol giving *N*-phenylacetamidinium picrate, m. p. 194—195° (Found: N, 19·3. Calc. for $C_{14}H_{13}O_7N_5$: N, 19·3%), higher than the values previously recorded (Part III). Yield, 91·6 g.

N-cyclo*Hexyl-αα-diethylacetamidine.**—When powdered aluminium chloride (10·6 g.) was added in one portion to 1-ethylbutyl cyanide (7·7 g.; Ziegler and Ohlinger, *Annalen*, 1932, **495**, 110) and *cyclo*hexylamine (9·6 g.; 1·2 mols.), the temperature rose to about 200°. When the temperature had fallen to 100°, the product was mixed with ice (100 g.) and the solid was collected and washed with a little ether. Recrystallisation of the solid (12 g.) from 0·5N-hydrochloric acid (125 c.c.) afforded 5·1 g. of N-cyclo*hexyl-αα-diethylacetamidinium chloride*, m. p. 240—242° (Found: N, 12·3. $C_{12}H_{25}N_2Cl$ requires N, 12·0%).

N-*Benzylbenzamidine.*—Aluminium chloride (13·3 g.) was added with stirring during 30 minutes to phenyl cyanide (10·3 g.) and benzylamine (10·7 g.) so that the temperature remained below 120°. After 20 minutes' heating at 180°, the amidine was isolated, collected in chloroform, and converted in aqueous solution into the hydrochloride, m. p. and mixed m. p. 227—229° (Part V). The yield of hydrochloride was 10·6 g., and 8·6 g. of *N*-benzylbenzamidinium picrate, m. p. 162—164°, were obtained from the mother liquor and sodium picrate solution. Recrystallisation from ethanol raised the m. p. of the picrate to 169—170° (Part V).

N-o-*Nitrophenylbenzamidine.*—*o*-Nitroaniline (13·8 g.) was dissolved in phenyl cyanide (10·3 g.) at 50°, finely powdered aluminium chloride (13·4 g.) was then added, and the mixture was stirred at 140°

* Preparation by Mr. J. Miller.

for 20 minutes. The amidine was liberated, collected in chloroform, dissolved in an equivalent of 5N-hydrochloric acid, and mixed with aqueous sodium picrate. Recrystallisation of the precipitate from aqueous cellosolve afforded N-o-*nitrophenylbenzamidinium picrate*, m. p. 208—209° (Found: N, 17·9. $C_{19}H_{14}O_9N_6$ requires N, 17·9%). Yield, 6·92 g.

N-2-*Pyridylbenzamidine*.—When aluminium chloride (6·7 g.) was added to a mixture of phenyl cyanide (5·15 g.) and 2-aminopyridine (4·7 g.) the temperature rose to 160° and the reaction was completed by heating at 200° for 15 minutes. Crystallisation of the crude amidine from light petroleum afforded N-2-*pyridylbenzamidine*, m. p. 99—99·5° (Found: N, 21·3. $C_{12}H_{11}N_3$ requires N, 21·3%). Yield, 6·1 g. The *picrate* crystallised from methanol in plates, m. p. 209° (Found: N, 19·9. $C_{18}H_{14}O_7N_6$ requires N, 19·7%), and the *toluene*-p-*sulphonate* had m. p. 171·5° (Found: N, 11·6. $C_{19}H_{19}O_3N_3S$ requires N, 11·4%).

N-*Phenylbenzamidine*.—A mixture of phenyl cyanide (5·2 g.), aniline (4·7 g.), and zinc chloride (6·8 g.) was heated at 110—115° for 30 minutes, and the temperature was then quickly raised to 210° to give a homogeneous melt, which was then cooled immediately. The crude amidine afforded 0·54 g. of *N*-phenylbenzamidine, m. p. and mixed m. p. 116° (Part I), on crystallisation from ethanol, and a second crop (2·5 g.), m. p. 112°, gave pure amidine (2·45 g.) when purified through the toluene-*p*-sulphonate.

N-*Benzylanisamidine*.—The temperature rose to about 200° when aluminium chloride (13·4 g.) was added to *p*-methoxyphenyl cyanide (13·3 g.) and benzylamine (11 g.). The product was crystallised from water giving N-*benzylanisamidinium chloride*, m. p. 225° (Found: N, 10·1. $C_{15}H_{17}ON_2Cl$ requires N, 10·1%). Yield, 22·8 g. N-*Benzylanisamidine* crystallised from light petroleum (b. p. 80—100°) in prisms, m. p. 89° (Found: N, 11·5. $C_{15}H_{16}ON_2$ requires N, 11·7%).

N-cyclo*Hexylanisamidine*.—*p*-Methoxyphenyl cyanide (6·65 g.), *cyclo*hexylamine (6·0 g.), and aluminium chloride (7 g.), brought into reaction as described in the previous example, afforded N-cyclo*hexylanisamidinium chloride* (12·6 g.), m. p. 275—276° (decomp.) (Found: N, 10·4. $C_{14}H_{21}ON_2Cl$ requires N, 10·4%). N-cyclo*Hexylanisamidine*, purified by sublimation in a vacuum, had m. p. 100° (Found: N, 12·3. $C_{14}H_{20}ON_2$ requires N, 12·1%), and the *picrate* crystallised from ethanol in needles, m. p. 141° (Found: N, 15·3. $C_{20}H_{23}O_8N_5$ requires N, 15·2%).

N-*Phenyl*-2:4-*dichlorobenzamidine*.—Powdered aluminium chloride (6·7 g.) was added during 10 minutes to a solution of 2:4-dichlorophenyl cyanide (8·6 g.) in aniline (4·7 g.) prepared at 50°. The temperature rose to *ca.* 130° during the addition and the reaction was completed by heating at 140° for an hour. The crude amidine (12·7 g.) was converted into N-*phenyl*-2:4-*dichlorobenzamidinium chloride* (11·1 g.), m. p. 147—149° (Found: N, 9·0. $C_{13}H_{11}N_2Cl_3$ requires N, 9·3%). Addition of sodium picrate to the mother liquors afforded the *picrate* (2·4 g.), m. p. 148—149° (Found: N, 13·9. $C_{19}H_{13}O_7N_5Cl_2$ requires N, 14·15%).

N-2-*Pyridyl*-p-*methylsulphonylbenzamidine*.—Aluminium chloride (4·5 g.; 0·7 mol.) was added with cooling to *p*-methylsulphonylphenyl cyanide (9·05 g.) and 2-aminopyridine (4·7 g.), and the mixture was then heated at 180° for 30 minutes. N-2-*Pyridyl*-p-*methylsulphonylbenzamidine* (10·1 g.) crystallised from methanol in colourless plates, m. p. 170·5° (Found: N, 15·5. $C_{13}H_{13}O_2N_3S$ requires N, 15·3%). The base afforded a *monopicrate*, m. p. 208—208·5° (Found: N, 16·4. $C_{19}H_{16}O_9N_6S$ requires N, 16·7%). Less than 0·1% of this amidine was produced when the cyanide and 2-aminopyridine benzenesulphonate (4 mols.) were heated at 224° for 5 hours.

N-cyclo*Hexylphenylacetamidine*.—(*a*) The addition of aluminium chloride (13·4 g.) to benzyl cyanide (11·7 g.) and *cyclo*hexylamine (9·9 g.) was regulated so that the temperature of the mixture did not exceed 140°, and the cold reaction product was decomposed by cold water (100 c.c.). The crude hydrochloride (22·7 g., m. p. 299—300° decomp.) was collected after cooling, and recrystallisation from water afforded N-cyclo*hexylphenylacetamidinium chloride*, m. p. 301—302° (decomp.) (Found: N, 11·0. $C_{14}H_{21}N_2Cl$ requires N, 11·1%). N-cyclo*Hexylphenylacetamidine* crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 122·5° (Found: N, 12·95. $C_{14}H_{20}N_2$ requires N, 13·0%). The *picrate* had m. p. 103—105° (Found: N, 15·9. $C_{20}H_{23}O_7N_5$ requires N, 15·7%). The effect of variations in the proportion of reactants and in the reaction conditions on the yield of amidine is shown in the table below. Each experiment was performed with 11·7 g. of benzyl cyanide, and variations in the reaction time were due to the necessity of controlling the temperature in some experiments by regulating the rate of addition of aluminium chloride and in others by heating the reaction mixture.

Benzylamine (mols.)	1	1	1	1	1	1	3	1	0·33
Aluminium chloride (mols.)	1	0·5	0·25	0·1	0·5	0·5	0·5	0·7	0·5
Temp.	140°	140°	140°	140°	80°	80° *	80°	15°	80°
Time, mins.	20	20	35	35	60	150	60	60	60
Yield of amidine, %	90	88	50	33	66	31	86	7·5	78 †

* Benzene (50 c.c.) was used as solvent. † Calculated on the amine.

(*b*) The temperature rose to *ca.* 60° when anhydrous zinc chloride (13·7 g.) was added to benzyl cyanide (11·7 g.) and *cyclo*hexylamine (9·9 g.), and after 2 hours at 200° *N-cyclo*hexylphenylacetamidine (1·2 g. or 6%), m. p. and mixed m. p. 122·5°, was isolated from the reaction product. After 30 minutes at 100° the yield of amidine was 5%.

N-cyclo*Hexyl*-1-*amidino*-n-*heptane*.—An exothermic reaction occurred when aluminium chloride (2·7 g.) was added to *n*-heptyl cyanide (2·5 g.) and *cyclo*hexylamine (2 g.), and the temperature rose to *ca.* 200°. The reaction mixture, which was allowed to cool immediately, afforded N-cyclo*hexyl*-1-*amidino*-n-*heptane hydrochloride* (5·1 g.), m. p. 200° (Found: N, 10·65. $C_{14}H_{29}N_2Cl$ requires N, 10·75%). The *picrate* had m. p. 102° (Found: N, 15·6. $C_{20}H_{31}O_7N_5$ requires N, 15·45%).

1:3-*Bis*-(N-*phenyl*-4-*amidinophenoxy*)*propane*.—Powdered aluminium chloride (2·67 g.; 1 mol.) was added during 10 minutes with stirring to a mixture of 1:3-bis-(4-cyanophenoxy)propane (5·6 g.) and aniline (3·7 g.; 2 mols.) previously heated to 140°, and, after 20 minutes at this temperature, the mixture was cooled and decomposed with hot aqueous alcohol. The crude amidine (6·4 g.) was

liberated and converted into 1 : 3-*bis*-(N-*phenyl*-4-*amidinophenoxy*)*propane benzenesulphonate*, m. p. 219—220° (Found: N, 7·3. $C_{41}H_{40}O_8N_6S_2$ requires N, 7·2%). The *amidine* had m. p. 206—207° (Found: N, 12·1. $C_{29}H_{28}O_2N_4$ requires N, 12·1%), and the *hydrochloride*, m. p. 287—288° (decomp.) (Found: N, 10·5. $C_{29}H_{30}O_2N_4Cl_2$ requires N, 10·4%).

NN-*Pentamethylenebenzamidine*.—Aluminium chloride (13·4 g.) was added during 20 minutes with cooling in ice-water to phenyl cyanide (10·3 g.) and piperidine (8·5 g.), and the mixture was subsequently heated on the steam-bath for 1½ hours. *NN*-Pentamethylenebenzamidine (6·9 g.), b. p. 98°/0·5 mm., was isolated from the product and converted into the picrate, m. p. and mixed m. p. 173—174° (Part IV).

N-*Phenyl*-N-*methylbenzamidine*.—Aluminium chloride (6·7 g.) was slowly added to phenyl cyanide (5·15 g.) and methylaniline (5·35 g.), and, after 20 minutes at 160°, *N*-phenyl-*N*-methylbenzamidine (10·5 g.) was isolated; it crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 85·5° (Found: N, 13·3. Calc. for $C_{14}H_{14}N_2$: N, 13·3%). The picrate had m. p. 187° (Found: N, 15·9. Calc. for $C_{20}H_{17}O_7N_5$: N, 15·9%). The m. p.s of the amidine and its picrate are recorded in Part V as 85° and 186—188° respectively.

NN-*Diethyl*-p-*methylsulphonylbenzamidine*.—A mixture prepared by slowly adding aluminium chloride (7 g.) to *p*-methylsulphonylphenyl cyanide (9·05 g.) and diethylamine (7·3 g.; 2 mols.) was heated on the steam-bath for 1½ hours, and afforded the crude amidine (12·8 g.) as a gum. NN-*Diethyl*-p-*methylsulphonylbenzamidinium picrate* had m. p. 184·5° (Found: N, 14·7. $C_{19}H_{21}O_9N_5S$ requires N, 14·5%), and the *toluene*-p-*sulphonate* had m. p. 162° (Found: N, 6·6. $C_{19}H_{26}O_5N_2S_2$ requires N, 6·6%).

NN-*Pentamethylene*-p-*methylsulphonylbenzamidine*.—(*a*) A mixture of *p*-methylsulphonylphenyl cyanide (9·05 g.), piperidine (8·5 g.; 2 mols.), and aluminium chloride (7 g.), prepared and heated as in the last example, afforded NN-*pentamethylene*-p-*methylsulphonylbenzamidine* (13·1 g.), m. p. 97° (Found: N, 10·4. $C_{13}H_{18}O_2N_2S$ requires N, 10·5%). The *picrate* was first obtained from methanol in slender needles, m. p. 199—199·5° (Found: N, 14·2. $C_{19}H_{21}O_9N_5S$ requires N, 14·5%), but a second form crystallising from the same solvent in cubic crystals, m. p. 188·5°, was subsequently obtained. The lower-melting form was converted into the needle form, m. p. 199·5°, at its m. p., and either could be obtained by inoculating a methanolic solution with a crystal of the desired form. The *toluene*-p-*sulphonate* crystallised from alcohol in prisms, m. p. 230—231° (Found: N, 6·5. $C_{20}H_{26}O_5N_2S_2$ requires N, 6·4%).

The following experiments, performed on a 0·025 g.-mol. scale using equimolecular proportions of the reactants, illustrate the influence of solvents on the yield of amidine. The yields are in terms of the picrate, m. p. 199·5°.

Solvent.	Nitrobenzene.	Chloroform.	Carbon tetrachloride.	Benzene.	
Vol., c.c.	20	25	25	25	25
Temp.	95°	65°	80°	85°	85°
Time, hrs.	1	2	2	2	6
Yield, %	25	15·2	25·0	56·5	60·5

(*b*) Triphenylaluminium, prepared from aluminium turnings (1 g., 2·7 atoms) and diphenylmercury (5 g.; 1 mol.) (cf. Hilpert and Gruttner, *Ber.*, 1912, **45**, 2828), was mixed with *p*-methylsulphonylphenyl cyanide (2·5 g.) and piperidine (1·2 g., 1 mol.). The temperature rose spontaneously to 125° and was maintained by heating for another 10 minutes. The crude amidine (1·7 g.) was isolated, and afforded the pure picrate (2·2 g., 32%), m. p. 199·5°.

(*c*) A solution of *p*-methylsulphonylphenyl cyanide (3·62 g.), piperidine (1·7 g.; 1 mol.), and triphenyl borate (5·8 g.; 1 mol.) in benzene (10 c.c.) was boiled for 2 hours (internal temp. 85°) and diluted with chloroform, and the amidine was extracted with dilute sulphuric acid. The yield of picrate, m. p. 199·5°, was 3·5%.

(*d*) The preparation of this amidine by the benzenesulphonate method is described above.

NN-*Diphenylpicolinamidine*.—2-Cyanopyridine (5·2 g.) and diphenylamine (8·5 g.) were warmed until a homogeneous mixture was obtained, and powdered aluminium chloride (6·7 g.) was then added with stirring, the temperature rising to 85°. The mixture was heated at 140° for 30 minutes and the amidine was then liberated and collected in chloroform. The crude amidine (10·4 g.; m. p. 116—118°) was crystallised several times from light petroleum and afforded NN-*diphenylpicolinamidine*, m. p. 129—130° (Found: N, 15·2. $C_{18}H_{15}N_3$ requires N, 15·4%). The *picrate* crystallised from methano in prisms, m. p. 164·5—165·5° (Found: N, 16·5. $C_{24}H_{18}O_7N_6$ requires N, 16·7%).

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210. *The Preparation of Benzylamines from Benzyl Halides and Hexamethylenetetramine.*

By JOHN GRAYMORE.

A new method for the preparation of cyclic methyleneimines and thence the corresponding primary amines is described, as is also a method for the preparation of benzylmethylamine. The work also shows that these methyleneimines may be converted into the corresponding aldehydes by heating with hydrochloric acid providing the methyleneimine be in excess.

VARIOUS investigators have described methods for the preparation of primary amines from hexamine–alkyl halides (Delépine, *Compt. rend.*, 1895, **120**, 501; *Bull. Soc. chim.*, 1897, **17**, 290;

Compt. rend., 1897, **124**, 292; Galat and Elion, *J. Amer. Chem. Soc.*, 1939, **61**, 3585). The present method depends on the preparation of a methyleneimine by decomposition of an aqueous solution of a quaternary compound such as hexamine–benzyl chloride in the presence of excess of ammonia, and subsequent hydrolysis of the cyclic methyleneimine by excess of hydrochloric acid :

$$6(CH_2)_6N_4,C_6H_5\cdot CH_2Cl + 8NH_3 \longrightarrow 3(C_6H_5\cdot CH_2\cdot N{:}CH_2)_2 + 5(CH_2)_6N_4 + 6NH_4Cl$$

$$3(C_6H_5\cdot CH_2\cdot N{:}CH_2)_2 + 6HCl + 6H_2O \longrightarrow 6C_6H_5\cdot CH_2\cdot NH_2,HCl + 6CH_2O$$

Hoch (D.R.-P. 139,394) showed that the oil obtained by adding excess of sodium hydroxide to hexamine–alkyl halides gave a cyclic methyleneimine when gently heated. The cyclic methyleneimine could not, however, be obtained directly by heating an aqueous solution of hexamine–alkyl halide with sodium hydroxide. Heated alone, an aqueous solution of the quaternary compound gives benzaldehyde (Sommelet, *Compt. rend.*, 1913, **157**, 852).

The ammonia serves the double purpose of ensuring the alkalinity of the solution, thus facilitating the polymerisation of the benzylmethyleneamine and so preventing its isomerisation to benzylidenemethylamine, and also combines with the liberated formaldehyde.

The hydrochlorides of benzylamine and of *p*-nitro-, *p*-chloro- and *m*-methyl-benzylamine were obtained. The molecular weight (Rast) of the solid methyleneimine, obtained either by the above method or by direct condensation of benzylamine with formaldehyde, indicated it to be a mixture of the dimeride and the trimeride of $CH_2{:}N\cdot CH_2Ph$, although it is possible that at the high temperature of melting camphor depolymerisation occurs. Analysis of the addition product of the methyleneimine with methyl iodide also seemed to indicate that the methyleneimine is a mixture. Decomposition of the addition product by heating with water at 80° gave the hydriodide of benzylmethylamine, a benzylmethyleneimine, formaldehyde, and a small quantity of a substance apparently the *methiodide* of the trimeride :

$$2(C_6H_5\cdot CH_2\cdot N{:}CH_2)_2,CH_3I + 2H_2O \longrightarrow 2C_6H_5\cdot CH_2\cdot NH\cdot CH_3,HI + (C_6H_5\cdot CH_2\cdot N{:}CH_2)_2 + CH_2O$$

The aqueous solution yields benzylmethylamine hydriodide. The method is thus suitable for providing the secondary amine pure and in good yield. The breakdown of quaternary derivatives obtained from the cyclic methyleneimines to give secondary amines has been demonstrated previously (Graymore, *J.*, 1938, 1311) but the above decomposition differs in that the secondary amine is readily recoverable by virtue of the fact that the other products, save formaldehyde, are insoluble in cold water.

It has been shown (Graymore, *J.*, 1945, 293), following a suggestion of Sommelet (*loc. cit.*), that the condensation product of benzylamine with formaldehyde, dissolved in hydrochloric acid, gave benzaldehyde when heated with hexamine. A similar result has now been achieved by heating the condensation product with two-thirds of the quantity of hydrochloric acid as required by the equation $(C_6H_5\cdot CH_2\cdot N{:}CH_2)_2 + 2HCl = 2C_6H_5\cdot CH_2\cdot N{:}CH_2,HCl$, the excess of cyclic methyleneimine replacing the hexamine previously used.

Experimental.

Cyclic Benzylmethyleneimine.—Hexamine–benzyl chloride (90 g.) was dissolved in water (400 c.c.) containing an excess of ammonia (70 c.c.; *d* 0·88) and the solution heated under reflux (1½ hours). Formaldehyde (20 c.c.; 40%) was now added to remove excess of ammonia and to precipitate any free benzylamine as cyclic methyleneimine. The oily cyclic base was allowed to settle, the greater part of the supernatant liquor decanted, and the residue poured into a large quantity of cold water; solidification of the oil was hastened by vigorous stirring. The solid was then ground, and washed well with cold sodium hydroxide and finally with cold water. The crude product (35—36 g.), *bis*(*benzylmethyleneimine*), recrystallised from cold benzene or light petroleum, had m. p. 46° and was identified by comparison with sample prepared directly from benzylamine and formaldehyde [Found : *M* (Rast), 254. $(C_6H_5\cdot CH_2\cdot N{:}CH_2)_2$ requires *M*, 238]. From the decanted liquor, 50 g. of a mixture of hexamine and ammonium chloride were recovered.

Benzylamine hydrochloride. The cyclic imine (10 g., crude), dissolved in excess of concentrated hydrochloric acid, was steam-distilled to remove formaldehyde and traces of benzaldehyde, and evaporated to small bulk; benzylamine hydrochloride crystallised in large plates (11 g.), m. p. and mixed m. p. 248—249°.

Benzaldehyde from the cyclic base. To the cyclic methyleneimine (10 g.) was added concentrated hydrochloric acid (6 c.c.) and the mixture was gently heated under reflux (1 hr.). The solution was now made strongly acid with dilute hydrochloric acid, refluxed for a minute, and the precipitated benzaldehyde removed by ether and identified; yield 4 c.c. (50%).

Bis-(*p-nitrobenzylmethyleneimine*).—Hexamine–*p*-nitrobenzyl bromide (60 g.) dissolved in water (300 c.c.) containing ammonia (60 c.c.; *d* 0·88), was heated under reflux until the semi-solid orange

liquid which separated had formed a buff or buff-orange solid (1½ hrs.); this was cooled, removed (yield 23 g.), ground, and recrystallised from hot benzene, forming small needles, m. p. 158°. It dissolved in dilute hydrochloric acid and was reprecipitated as a buff powder. It was slightly soluble in alcohol but very soluble in ethyl acetate [Found: C, 58·5; H, 5·0; N, 16·8; *M* (Rast), 329. $(C_8H_8O_2N_2)_2$ requires C, 58·5; H, 4·9; N, 17·07%; *M*, 328].

(i) This *dimer* (14 g.) was dissolved in excess of hydrochloric acid (20 c.c., *d* 1·19, in 200 c.c. of water). Steam-distillation removed most of the formaldehyde, and the solution on concentration yielded *p*-nitrobenzylamine hydrochloride in yellow crystals (15 g., crude). Most of the yellow colour was extracted by washing with a small quantity of warm alcohol, and recrystallisation from water afforded needles decomposing at 256° (Found: Cl, 18·8. Calc. for $C_7H_8O_2N_2$,HCl: Cl, 18·8%).

(ii) To the cyclic methyleneimine (6 g.) was added hydrochloric acid (*d* 1·19; 2·6 c.c.) and the mixture was gently refluxed (¼ hr.). After addition of an excess of dilute hydrochloric acid with cooling, *p*-nitrobenzaldehyde separated (0·8 g.); a further quantity was obtained on dilution of the filtrate with water. Recrystallised from hot water, it was obtained as a pale yellow substance, m. p. 106°, identified by conversion into its 2 : 4-dinitrophenylhydrazone.

Decomposition of Hexamine–p-Chlorobenzyl Chloride.—The quaternary compound (30 g.), dissolved in water (100 c.c.) containing ammonia (*d* 0·88; 30 c.c.), was heated under reflux (1 hr.). After cooling, the supernatant liquor was decanted from the oily methyleneimine, the latter washed several times with water, extracted with ether, and dried over solid sodium hydroxide. After removal of the ether, the base p-*chlorobenzylmethyleneimine* was distilled under reduced pressure and obtained as a viscous oil, b. p. 220°/100 mm. (Found: C, 62·5; H, 5·21. C_8H_8NCl requires C, 62·6; H, 5·2%). The molecular weight was not determined.

(i) This imine (6 g.) was dissolved in excess of hydrochloric acid, steam-distilled to remove formaldehyde, and evaporated to small bulk, *p*-chlorobenzylamine hydrochloride crystallising out on cooling; recrystallised from alcohol, it melted at 250° (6 g.) (Found: N, 7·9. Calc. for C_7H_8NCl,HCl: N, 7·9%).

(ii) To the imine (6 g.) was added hydrochloric acid (*d* 1·19; 3 c.c.), and the mixture was heated gently under reflux (10 mins.). Excess of hydrochloric acid was now added, and boiling continued for 5 mins. On cooling, *p*-chlorobenzaldehyde separated as an oil which was extracted with ether. On removal of the ether it solidified (yield 2·5 g.). It was identified by oxidation to *p*-chlorobenzoic acid, m. p. and mixed m. p. 236°.

m-*Methylbenzylamine Hydrochloride.*—To hexamine–*m*-methylbenzyl bromide (25 g.), dissolved in water (100 c.c.), was added ammonia (*d* 0·88; 30 c.c.), and the solution heated under reflux (1 hr.). The syrupy oil which separated was removed, washed with cold water, dissolved in excess of hydrochloric acid, steam-distilled to remove formaldehyde, and the solution concentrated. *m*-Methylbenzylamine hydrochloride separated, and recrystallised from water in needles (7 g.) (Found: Cl, 22·5. Calc. for $C_8H_{12}NCl$: Cl, 22·5%).

cyclo*Hexylmethyleneimine.*—Addition of *cyclo*hexylamine (50 g.) slowly to formaldehyde (40 c.c., 40%) precipitated an oil which solidified. From alcohol it crystallised in long prisms, m. p. 75° [Found: C, 75·1; H, 11·7; N, 12·7; *M* (Rast), 144. $C_7H_{13}N$ requires C, 75·6; H, 11·7; N, 12·6%; *M*, 111. $C_6H_{11}N{:}CH_2$ requires *M*, 111].

Benzylmethyleneimine Methiodide.—To benzylmethyleneimine [1 mol. calculated as $(C_6H_5{\cdot}CH_2{\cdot}N{:}CH_2)_3$], recrystallised from light petroleum and dissolved in dry ether, was added methyl iodide (1½ mols.). After one day the precipitated *methiodide* was filtered off [Found: C, 59·1; H, 5·32; N, 8·1; I, 27·4. $(C_6H_5{\cdot}CH_2{\cdot}N{:}CH_2)_2{\cdot}CH_3I$ requires C, 53·7; H, 5·5; N, 7·37; I, 33·4%. $(C_6H_5{\cdot}CH_2{\cdot}N{:}CH_2)_3{\cdot}CH_3I$ requires C, 60·1; H, 6·0; N, 8·4; I, 25·5%].

Hydrolysis of Cyclic Benzylmethyleneimine Methiodide: Preparation of Benzylmethylamine Hydriodide.—The foregoing addition compound (18 g.) was suspended in water (250 c.c.) in an open vessel and heated at 70—80° for one hour. The methiodide slowly decomposed, a sticky oil was deposited, and formaldehyde was evolved. On cooling, the oil partly solidified and a small quantity of a white solid (A, see below) separated in needles (slightly soluble in hot water). The filtrate was evaporated on the water-bath to dryness, formaldehyde being evolved, and gave benzylmethylamine hydriodide in yellow needles (9 g., crude). Crystallised from hot alcohol (twice), it formed white needles, m. p. 164° (Emde, *Arch. Pharm.*, 1909, **247**, 364, gives m. p. 124°) (Found: C, 38·7; H, 4·8; N, 5·3; I, 51·2. Calc. for $C_8H_{12}NI$: C, 38·6; H, 4·8; N, 5·6; I, 51·0%). It was further identified by conversion into *p*-toluenesulphonbenzylmethylamide, m. p. 92—93° (Found: S, 11·4. Calc. for $C_{15}H_{17}O_2NS$: S, 11·6%). The residue (A, above) was ground, and extracted with ether. The ethereal solution yielded cyclic benzylmethyleneimine, m. p. 46° (4 g.) [Found: C, 80·6; H, 7·6; *M* (Rast), 242. Calc. for $(C_8H_9N)_3$: C, 80·6; H, 7·6%; *M*, 238]. The residue from the ethereal extract recrystallised from hot alcohol in needles, m. p. 160—161°, of the *methiodide* of tris(benzylmethyleneimine) (4 g.) (Found: I, 25·3; N, 8·17. $C_{25}H_{30}N_3I$ requires I, 25·5; N, 8·4%). Heated with water at 80°, it decomposed slowly to give benzylmethylamine hydriodide, formaldehyde, and cyclic benzylmethyleneimine. At higher temperatures under reflux a small quantity of benzaldehyde is formed.

Analysis and molecular-weight determinations were by Drs. Weiler and Strauss.

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211. *The Kinetics of the Reaction between Copper and Iodine in Various Solutions. Part II. Solutions of Iodine in Organic Solvents.*

By L. L. Bircumshaw and M. H. Everdell.

The kinetics of the reaction between copper and iodine when dissolved in carbon tetrachloride, chloroform, benzene, or diamyl ether has been investigated. In carbon tetrachloride and chloroform the rate appears to follow the equation $dx/dt = k(a - x)/x$, where the symbols have their usual significance. The influence of the state of the surface of the copper and the temperature coefficient has also been studied. Whereas in the work (Part I) on aqueous (potassium iodide) solutions of iodine it was shown for a large range of iodine concentrations that the rate of reaction is unaffected by the presence or thickness of the film of cuprous iodide, yet with the above solutions the rate appears to be partly controlled by the thickness of the iodide film.

In Part I (*J.*, 1942, 598) the results of a study of the rate of reaction of copper on iodine in aqueous (potassium iodide) solution were communicated. It was shown that for a large range of iodine concentration the reaction was unimolecular with respect to the iodine concentration, and the rate was unaffected by the presence or absence of a cuprous iodide film or by the method of preparation or degree of smoothness of the copper surface. The increase in reaction rate found on increasing the potassium iodide concentrations to very high values was identified with the increase in the rate of diffusion of iodine in these circumstances. It was also demonstrated that the reaction proceeds by the diffusion of both iodine and solvent through the cuprous iodide film and not by the diffusion of copper ions.

It is well known that iodine dissolved in aqueous potassium iodide is present largely in the form of the complex ion I_3^-, the proportion of free iodine molecules being very small. In the case of organic solvents giving violet solutions the iodine is considered to exist as simple molecules, whereas in the brown solutions obtained with ethers, ketones, or esters it exists mainly as a co-ordination complex with the solvent. The great difference in the state of the iodine in aqueous solutions on the one hand, and in organic solvents on the other, might be expected to have a considerable effect on the kinetics of the reaction between copper and iodine, and it was decided to extend the work to solutions of the latter type.

This work may be divided into the following sections: (1) Experiments carried out between copper and iodine in carbon tetrachloride solution at 25°. The initial concentration of the solutions varied from 0·0025 to 0·04 g.-atom/l. (2) Experiments at 25° in chloroform, benzene, and diamyl ether, showing the effect of change of solvent. (3) Experiments at 0°, 25°, and 30°, showing the effect of change of temperature. (4) Experiments at 25°, showing the influence of the state of the copper surface on the rate of reaction.

Experimental.

The experimental method has been described (Part I, *loc. cit.*). Briefly it consisted in rotating strips of thick copper foil of 36 sq. cm. area in the iodine solution at about 100 revs./min. The course of the reaction was followed by titration: 5 c.c. of the solution were pipetted into an excess of N/1600-sodium thiosulphate solution, shaken until all the iodine had reacted, and then back-titrated with N/1600-iodine solution. The copper strips showed a firm film of whitish-brown cuprous iodide which exhibited no crumbling.

Carbon tetrachloride. "AnalaR" Carbon tetrachloride was distilled over calcium chloride and then repeatedly over clean, polished strips of copper to remove any traces of sulphur present. Fractions boiling at 76·7° were used for the work. The results are given in Table I, where $k = \frac{2{\cdot}303v}{t_2 - t_1} \log_{10} \frac{C_1}{C_2}$ and χ is given in g.-atoms $\times 10^6$, all the data relating to 25°.

Col. 7 in the readings for initial concentration N/400, contains the values of the simple unimolecular constant k (corrected for the volume change). In the reaction for copper with iodine in aqueous (KI) solution a constant is given by this equation, but in the present experiments it is seen that k falls rapidly with time. This suggests that the reaction is retarded by the cuprous iodide film. However, that the Tammann–Pilling–Bedworth equation $\chi^2 = kt$ is not obeyed is seen by an examination of Fig. 1, where χ is plotted against time. If this relation were obeyed, values of χ for a particular time t should all be equal and independent of the initial concentration of the iodine. It can also be seen that the ordinates are not proportional to the iodine concentration, which should be the case if the unimolecular relation is obeyed. It appeared probable that this reaction in organic media (*a*) was proportional to the iodine concentration, and (*b*) was inversely proportional to the thickness of the cuprous iodide film formed on the copper. Hence, if a = initial concentration of iodine and $a - x$ = concentration of iodine at time t,

$$dx/dt = k(a - x)/x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

since x is proportional to the thickness of the cuprous iodide film. The integrated form of this equation, giving k, the velocity constant, will only hold for the reaction at constant volume. In the present work

TABLE I.

Time, mins.	$(a-x)$.	[I], C.	x.	χ.	k_n.	k.
		300 C.c. of N/400-iodine in CCl_4.				
0	20·0	0·0025	—	—	—	—
10	17·5	0·00219	2·5	2·60	0·192	4·01
20	16·2	0·00202	3·8	3·94	0·265	2·28
30	15·5	0·00194	4·5	4·64	0·193	1·28
60	13·9	0·00174	6·1	5·52	0·196	1·03
90	12·65	0·00158	7·35	6·73	0·206	0·88
150	11·15	0·00139	8·85	8·17	0·161	0·58
					Mean 0·202	

Time, mins.	$(a-x)$.	[I], C.	x.	χ.	k_n.
	300 C.c. of N/200-iodine in CCl_4.				
0	20·0	0·005	—	—	—
10	18·2	0·0045	1·8	3·75	0·194
20	17·65	0·00441	2·35	4·877	0·140
30	17·15	0·00429	2·85	5·884	0·134
60	16·1	0·00402	3·9	7·962	0·149
120	14·3	0·00357	5·7	11·462	0·193
180	12·9	0·00322	7·1	14·135	0·217
				Mean	0·171

Time, mins.	$(a-x)$.	[I], C.	x.	χ.	k_n.
	300 C.c. of N/50-iodine in CCl_4.				
0	20·0	0·020	—	—	—
10	19·2	0·0192	0·8	6·67	0·150
25	18·7	0·0187	1·3	10·77	0·162
50	18·15	0·0181	1·85	15·2	0·165
100	17·35	0·0173	2·65	21·5	0·170
160	16·7	0·0167	3·3	16·6	0·187
250	16·0	0·0160	4·0	31·9	0·162
390	15·0	0·0150	5·0	39·4	0·183
					Mean 0·169

	300 C.c. of N/100-iodine in CCl_4.				
0	20·0	0·01	—	—	—
10	18·75	0·00937	1·25	5·25	0·185
20	18·25	0·00912	1·75	7·26	0·181
30	17·85	0·00892	2·15	8·69	0·174
60	16·95	0·00847	3·05	12·51	0·196
120	15·6	0·00780	4·4	17·60	0·205
180	14·5	0·00725	5·5	21·80	0·197
270	13·4	0·00670	6·6	25·93	0·193
390	12·3	0·00615	7·7	29·97	0·179
600	10·8	0·00540	9·2	35·39	0·177
				Mean	0·187

	300 C.c. of N/25-iodine in CCl_4.				
0	20·0	0·040	—	—	—
8	19·5	0·0390	0·5	8·33	0·144
40	18·8	0·0376	1·2	19·8	0·172
80	18·3	0·0366	1·7	17·9	0·167
140	17·7	0·0354	2·3	36·0	0·186
220	17·1	0·0342	2·9	45·3	0·183
					Mean 0·170

the volume of the reacting liquid varies with each reading owing to the extraction of 5·0 c.c. for the titration. The immediate problem is to insert this volume correction into equation (1).

If m is the mass of iodine in solution, and c and v are the concentration and volume respectively, then $m = cv$ and

$$-\mathrm{d}m/\mathrm{d}t = -\mathrm{d}(cv)/\mathrm{d}t$$

If c_0 = initial concentration and v_0 = initial volume then

$$-\mathrm{d}(cv_0)/\mathrm{d}t = kc/v_0(c_0 - c)$$

because $v_0(c_0 - c)$ is proportional to the thickness of the cuprous iodide film at any moment during the first interval; hence

$$k_1 = \frac{v_0^2}{t_1 - t_0}\left(c_0 \ln \frac{c_0}{c_1} - c_0 + c_1\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

At t_1, we remove 5 c.c., and with the new volume v_1 we have

$$-v_1\frac{\mathrm{d}c}{\mathrm{d}t} = \frac{kc}{v_0(c_0 - c_1) + v_1(c_1 - c)}$$

because $v_0(c_0 - c_1)$, now constant, represents the thickness of the film at the beginning of the second interval. Additional amounts of iodine added during the second stage are represented by $v_1(c_1 - c)$. Integrating between the limits c_1 and c_2 and t_1 and t_2, we have

$$k_2 = \frac{v_1v_0(c_0 - c_1)\ln(c_1/c_2) + v_1^2c_1\ln(c_1/c_2) - v_1^2(c_1 - c_2)}{t_2 - t_1} \quad . \quad . \quad . \quad . \quad . \quad (3)$$

This equation gives k_2, the velocity constant for the second interval. Similarly for the third interval we have

$$-v_2\frac{\mathrm{d}c}{\mathrm{d}t} = \frac{kc}{v_0(c_0 - c_1) + v_1(c_1 - c_2) + v_2(c_2 - c)}$$

which, integrated between the limits t_2 and t_3 and c_2 and c_3, gives

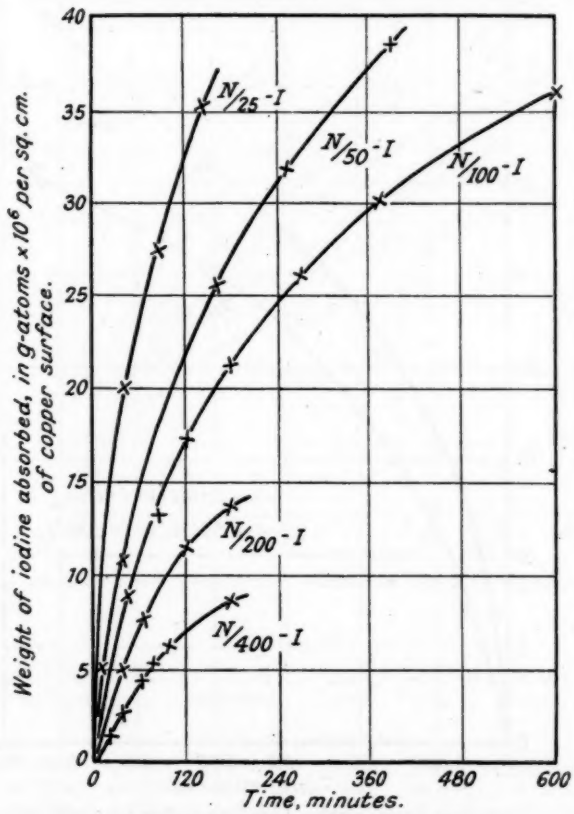
$$k_3 = \frac{v_2\{v_0(c_0 - c_1) + v_1(c_1 - c_2)\}\ln(c_2/c_3) + v_2^2c_2\ln(c_2/c_3) - v_2^2(c_2 - c_3)}{t_3 - t_2} \quad . \quad . \quad . \quad (4)$$

the velocity constant for the third interval. For the nth interval we have,

$$k_n = \frac{v_{n-1}\{v_0(c_0 - c_1) + v_1(c_1 - c_2) + \ldots v_{n-2}(c_{n-2} - c_{n-1})\} \ln (c_{n-1}/c_n)}{t_n - t_{n-1}} + \frac{v^2_{n-1}\, c_{n-1} \ln (c_{n-1}/c_n) - v^2_{n-1}(c_{n-1} - c_n)}{t_n - t_{n-1}} \quad . \quad (5)$$

From equation (5) we can calculate k for any interval (corrected for the change of volume). It is noteworthy that if equation (2) is used for all intervals in the reaction the differences shown in the values of the constant so obtained are small, *i.e.*, the correction term for the change of volume is small. That equation (5) is similar to equation (2), save for the inclusion of the volume changes in (5), may be shown by putting $v_1 = v_2 = v_3 \ldots = v_n$ in equation (5), whereupon it reduces to equation (2). The values of k_n are given in Table I. They are fairly constant, but the agreement is not excellent. When the average values are compared for different initial concentrations of iodine they show no regular drift.

FIG. 1.



Iodine in carbon tetrachloride at 25°.

A direct contrast between the reaction in aqueous potassium iodide and that in carbon tetrachloride can therefore be made. In the former case the reaction appears to be independent of the presence or thickness of the cuprous iodide film, whereas in the latter case the reaction is directly controlled by the film thickness.

The Effect of the Solvent on the Reaction Rate.—In the determination of the effect of the solvent on the rate four organic liquids have been used.

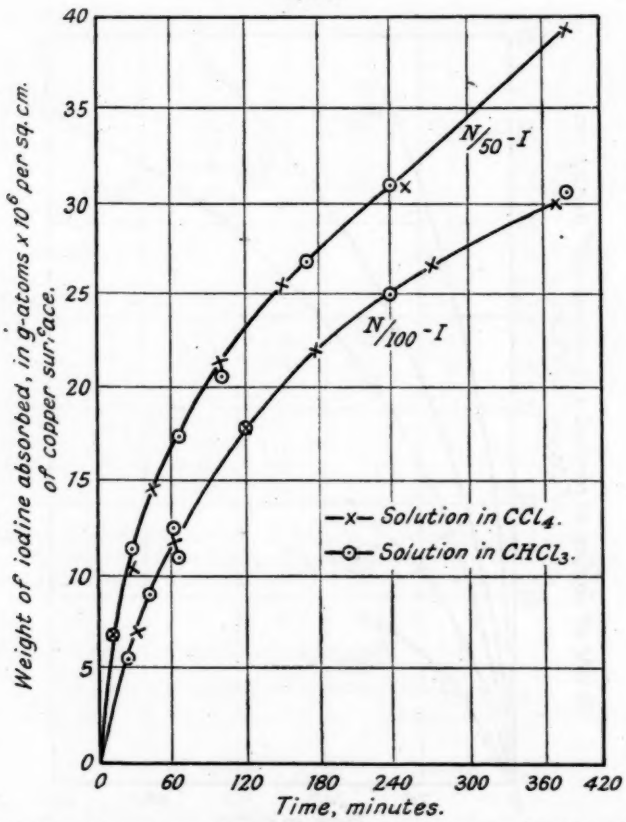
"AnalaR" Chloroform containing no foreign matter detectable by analysis (free acid, Cl^-, Cl_2, CHO, $COCl_2$) was kept over calcium chloride for 36 hours, decanted, and distilled. The first fractions were discarded, and the bulk of the liquid, b. p. 60·2°, reserved for the experiments. Data were obtained for two concentrations of iodine, N/100 and N/50. The results are shown in Fig. 2, and it is seen that the rates in carbon tetrachloride and in chloroform are practically identical.

"AnalaR" Benzene containing 0·001% of thiophen and 0·002% of non-volatile matter was kept over copper foil for several days and then over fused calcium chloride. After decantation the liquid was distilled, and further purified by freezing. The m. p. of the final fraction was 5·5°, and this was used for the work. The copper surface was prepared by carborundum straight polishing (Part I, *loc. cit.*). Preliminary experiments showed that the rate in benzene is less than in carbon tetrachloride,

so experiments were carried out over a range of concentration N/400—N/25. The results are shown graphically in Fig. 3, and it is seen that for concentrations greater than and including N/100 the rate of reaction in benzene is less than that in carbon tetrachloride; moreover, the difference in rate for the same concentration in the different solvents increases with increasing concentration. For solutions of N/200-iodine the rate in benzene is slightly greater than in carbon tetrachloride, and this difference is more pronounced in the case of N/400-solutions.

The solutions of iodine in certain oxygen-containing organic liquids, *e.g.*, ethers, esters, and ketones, show a deep brown colour when concentrated, changing to red at high dilutions. It is usually supposed that in such solutions co-ordination compounds exist between iodine and the solvent, the oxygen in the solvent acting as a donor element. It was desired to use such a solvent for this reaction. Of the common esters, ethers, and ketones, none is suitable. Acetone, which reacts with iodine in the presence of traces of alkali, was considered unsafe; diethyl ether and ethyl acetate have relatively high vapour pressures at 25°, and with the apparatus used, evaporation troubles would be encountered. The liquid

FIG. 2.



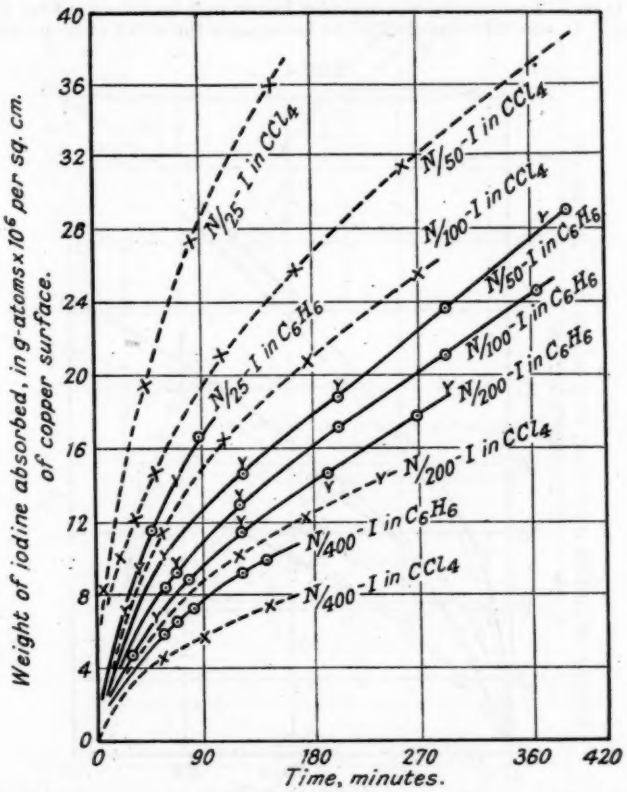
Comparison of reaction rates in chloroform and carbon tetrachloride at 25°.

eventually selected was diamyl ether. This, except for the reversible complex formation, is without action on iodine. Diamyl ether, obtained in large quantities, was purified by standing over calcium chloride, then copper foil, and by repeated distillation. The fraction of b. p. 168° was reserved for the experiments. It was intended to follow the course of the reaction in the usual way, *i.e.*, by titration, but this was found to be impossible, for the iodine in diamyl ether appears to react very slowly with sodium thiosulphate solution (possibly the dissociation of the iodine complex is very slow). On this account the rate was investigated gravimetrically. Copper strips were cut, polished, dried, and weighed. After reaction, the strip with the cuprous iodide film was washed well with diamyl ether, dried, and weighed again. The difference in weight gives the amount absorbed by the copper as cuprous iodide in time *t*. A new sheet of copper and a new solution of iodine were used for each experiment. The results are given in Table II, and the increases in weight are the means of two identical experiments; the iodine absorbed (col. 5) is given in terms of g.-atoms $\times 10^6$ per sq. cm. of surface. The strips could be very accurately cut, and the slight variations in weight are due to slight variations in thickness. It can be seen that at all concentrations the rate in diamyl ether is much less than the rate in carbon tetrachloride.

Effect of Temperature.—The temperature coefficient of the reaction between copper and iodine in aqueous (potassium iodide) solution is small, but large enough to permit accurate measurement of the change of rate due to 5° increase to be taken. It was intended to study the reaction in organic solvents

at 20°, 25°, 30° and 35°. Preliminary experiments showed, however, that the rate of reaction at 30° was very little greater than at 25°. The increase was too small to be shown accurately, and as it was undesirable to work at temperatures much above 25° it was decided to work at 0°. In this case, extreme

FIG. 3.



Comparison between rates of reaction in benzene and carbon tetrachloride at 25°.

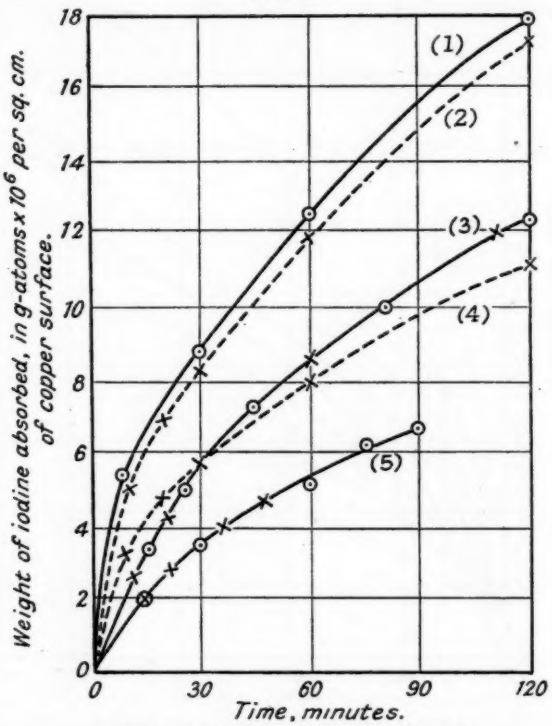
TABLE II.

Time, mins.	Initl. wt. of Cu, g.	Wt. of Cu +Cu_2I_2, g.	Increase, g.	I absorbed.	Time, mins.	Initl. wt. of Cu, g.	Wt. of Cu +Cu_2I_2, g.	Increase, g.	I absorbed.
				N/50-Iodine.					
15	4·1900	4·2069	0·0169	3·696	60	4·1802	4·2110	0·0308	6·736
30	4·1580	4·1810	0·0230	5·031	75	4·1905	4·2240	0·0335	7·326
45	4·1827	4·2101	0·0274	5·992	90	4·1852	4·2210	0·0358	7·830
				N/200-Iodine.					
15	4·1906	4·2022	0·0116	2·537	75	4·2134	4·2386	0·0252	5·511
30	4·3256	4·3425	0·0169	3·696	90	4·2616	4·2890	0·0274	5·992
45	4·2016	4·2217	0·0201	4·396	105	4·1558	4·1850	0·0292	6·386
60	4·1724	4·1950	0·0226	4·942	120	4·0154	4·1372	0·0318	6·955
				N/100-Iodine.					
15	4·2044	4·2200	0·0156	3·441	75	4·1606	4·1897	0·0291	6·364
30	4·0996	4·1185	0·0195	4·264	90	4·1324	4·1636	0·0312	6·823
45	4·1678	4·1915	0·0237	5·183	105	4·1564	4·1906	0·0342	7·480
60	4·2110	4·2376	0·0266	5·817	120	4·1888	4·2258	0·0370	8·092

care was taken to ensure the sealing of the reaction vessel, since at 0° the introduction of air would lead to water-vapour condensation. The temperature coefficient was investigated in this way with carbon tetrachloride and chloroform. The results are shown in Fig. 4, and it will be seen that the coefficient is very small.

Effect of Surface Condition of the Copper on the Rate.—The presence of an oxide film or different methods of preparing the surface of the metal have no effect on the rate of reaction in aqueous (KI) solution. It has been shown also that the rate of reaction in such solutions under the conditions studied is independent of the presence or thickness of the cuprous iodide layer on the copper. For reactions in carbon tetrachloride and chloroform it has been shown that the reaction is controlled by diffusion through the cuprous iodide layer. The structure of the film might well be influenced by the condition of the surface of the copper. It was therefore decided to investigate the effect of the condition of the surface on the rate.

FIG. 4.



Effect of temperature on rate of reaction.

(1) N/100-I *in* CCl_4 *at* 30°.
(2) N/100-I *in* CCl_4 *at* 25°.
(3) N/100-I *at* 0°: { × *in* CCl_4. ○ *in* $CHCl_3$.
(4) N/200-I *in* CCl_4 *at* 25°.
(5) N/200-I *at* 0°: { × CCl_4. ○ $CHCl_3$.

The four different methods of preparing the surface have been described in Part I (*loc. cit.*), *i.e.*, (i) carborundum straight polishing, (ii) carborundum circular polishing, (iii) mirror finish with jeweller's rouge, (iv) etching with dilute nitric acid.

These experiments were all carried out in benzene solution, as it was considered that the films in benzene appeared rather more even and less liable to flaking than in other solvents. The results are shown in Fig. 5. Only slight differences could be detected, but it can be seen that: (1) The rates in the case of carborundum straight and carborundum circular polishing are identical; (2) the rate on the mirror surface is slightly less, (3) the acid-etched surface gives an even lower reaction rate. That is, the rate is less with the smooth surfaces, coarseness of abrasion tending to increase the velocity of the reaction.

The presence of an oxide film on the copper. Copper strips of the correct area were polished by carborundum straight polishing and heated to 100° for 30, 20, and 10 mins. as described in Part I. The oxidised copper was placed in the reaction vessel, and the reaction followed in the usual way by titration. The results are shown in Fig. 6, and it will be seen that the rate in both carbon tetrachloride and benzene is considerably decreased by the presence of an oxide film.

Films formed in Aqueous and Organic Solvents.—It has been shown that for a large range of iodine concentrations the rate of reaction in aqueous solution is unaffected by the presence or thickness of the cuprous iodide film on the copper, whereas in the case of reactions carried out in organic solvents this film controls the reaction. The question arises as to whether this difference is due to a difference in the actual films formed in the two cases or to the nature of the solutions in the two different classes of solvent.

Strips of copper foil of the usual size were polished and then rotated in a solution of N/200-iodine in N/50-potassium iodide for 30 minutes. The strips of copper covered with cuprous iodide film were then removed from the solution and washed and dried carefully. Some of the strips showed small cracks in

FIG. 5.

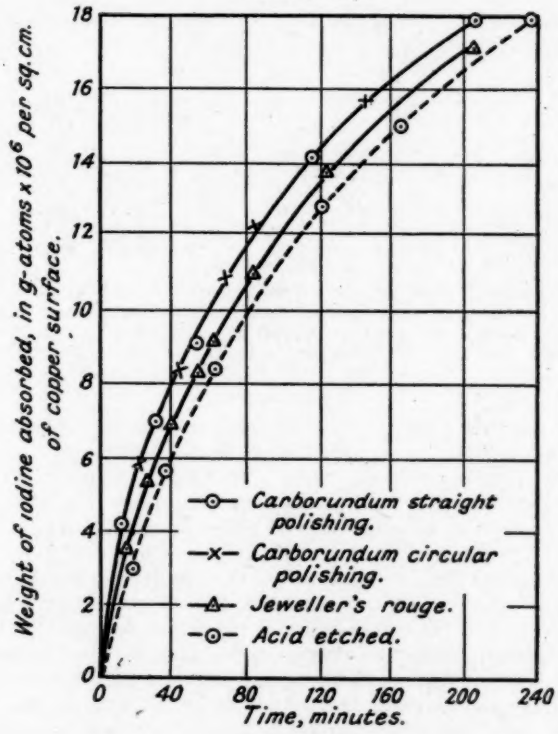
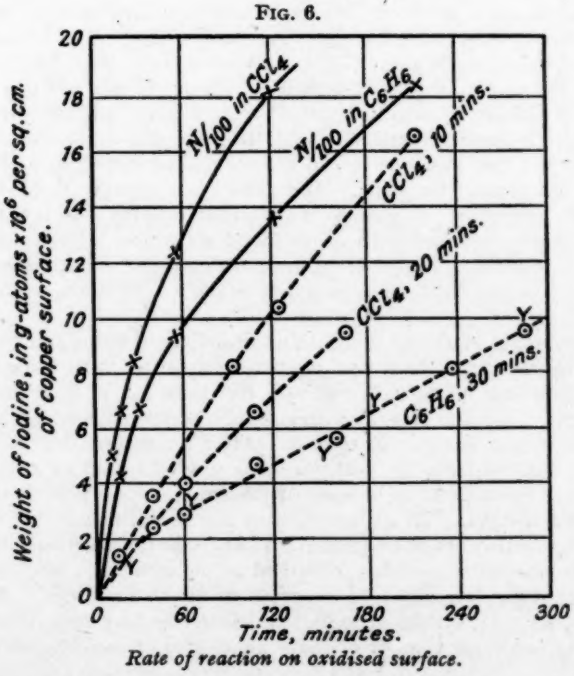

Weight of iodine absorbed, in g-atoms x 10⁶ per sq.cm. of copper surface.
Time, minutes.
Carborundum straight polishing.
Carborundum circular polishing.
Jeweller's rouge.
Acid etched.

FIG. 6.


Weight of iodine, in g-atoms x 10⁶ per sq.cm. of copper surface.
Time, minutes.
N/100 in CCl4
N/100 in C6H6
CCl4, 10 mins.
CCl4, 20 mins.
C6H6, 30 mins.

Rate of reaction on oxidised surface.

the films on drying and these were discarded. The "perfect" strips were then rotated in carbon tetrachloride, and the reaction followed by titration in the usual way. The results are given in Table III, (1) and (2), where χ is expressed as g.-atoms of I $\times 10^6$.

TABLE III.

(1) *Copper covered by cuprous iodide film formed in aqueous solution rotated in* N/200-*iodine in carbon tetrachloride at* 25°.

Time, mins.	10	20	30	60	120	180
χ_0	0·83	1·45	1·85	3·04	5·57	7·48
χ (no previous film)	3·75	4·88	5·88	7·96	11·46	14·135

(2) *Copper covered by cuprous iodide film formed in carbon tetrachloride solution rotated in* N/200-*iodine solution at* 25°.

Time, mins.	2	5	10	15	20	30	40	50	60
χ_0	1·67	4·33	8·56	12·12	15·43	20·58	24·71	27·65	30·00
χ (no previous film)	1·87	4·54	8·57	12·13	15·43	20·78	24·91	28·04	30·38

The results described under (1) were not very reproducible owing to a certain amount of film-cracking, but they clearly showed that the rate in carbon tetrachloride solution is much decreased by the presence on the metal of a film deposited from an aqueous solution. The results described under (2) were easily reproducible and it is seen that the rate is unaffected by the presence of a cuprous iodide film formed in carbon tetrachloride.

DISCUSSION.

The actual rate of reaction observed in these experiments probably depends ultimately on the collisions of the iodine molecules on the copper surface, whatever the means by which the iodine travels through the cuprous iodide film. The rate of diffusion of the iodine molecules through the film will be a function of the concentration gradient of the molecules across the film, *i.e.*, the concentration of an adsorbed film of iodine on the liquid side of the cuprous iodide and the concentration, much lower, of iodine at the film (Cu_2I_2)–metal interface. The concentration of the adsorbed film of iodine will obviously depend on the state of the iodine in solution. Lachmann (*J. Amer. Chem. Soc.*, **1903**, **25**, 50), after an examination of iodine solutions in 60 organic solvents, distinguished two types of solution: (1) violet solutions from substances like carbon tetrachloride, chloroform, etc. (substances called saturated by Lachmann); (2) brown solutions from ethers, esters, alcohols, and ketones (substances called unsaturated by him). This subject has been investigated by a number of workers but on the whole there seems to be little doubt that Lachmann's original classification was correct.

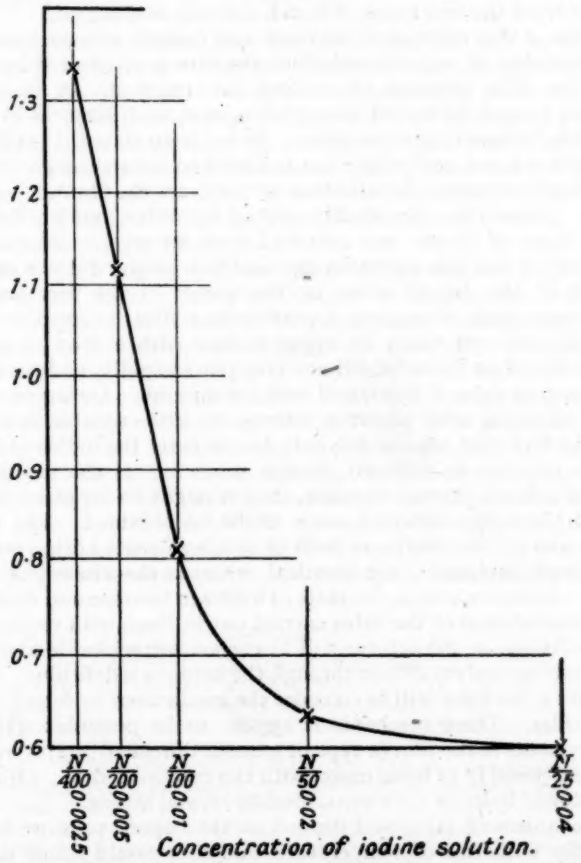
The problem of the benzene solution of iodine is not so simple, and on the collected evidence as a whole these solutions seem to fall directly into neither class. The problem has been investigated in recent years by Walker (*Trans. Faraday Soc.*, **1935**, **31**, 1432). This solution was placed by both Lachmann and by Getman (*J. Amer. Chem. Soc.*, **1928**, **50**, 2883) in the violet group, yet the colour is definitely reddish and very different from that in carbon tetrachloride, especially in concentrated solution: in more dilute solution the colours are more alike. From a study of the absorption spectrum, Walker concluded that there was some interaction between iodine and benzene. Hildebrand and Jenks (*ibid.*, **1920**, **42**, 2180) also showed that benzene solutions of iodine are abnormal with respect to their solubility–temperature relationships compared with other violet solutions. The problem of the possible solvation of iodine in benzene solution is made more complex by the fact that the resulting dipole moment is zero; yet when the evidence as a whole is considered some type of interaction seems to be indicated.

Some simple experiments made by the authors are not without significance. The solutions in carbon tetrachloride or chloroform can be titrated readily with sodium thiosulphate, the end-point being reached with no period of delay; but if 20 c.c. of an N/100-iodine solution in diamyl ether are titrated with N/100-thiosulphate in the presence of starch, the blue colour fades after the addition of a few c.c. of titrant. After about one hour's standing the colour returns, but is again dispersed by the addition of a small amount of thiosulphate, returning again after standing. The theoretical volume of thiosulphate solution required for titration is reached only after several days. This suggests that the thiosulphate only reacts with the free iodine, and that the restoration of the equilibrium between the latter and the complex is slow. If with benzene a solvent–iodine complex is formed in the same way and the complex is of the same nature, the same difficulty might be expected in direct titrations. No such difficulty is experienced, however, so that, although iodine and benzene may form some sort of complex, it is not of necessity of the same type or of the same degree of stability as those formed in the brown solutions.

It is seen in Fig. 2 that the rates of reaction in carbon tetrachloride and chloroform are identical. This is in agreement with Evans and Bannister's results (*Proc. Roy. Soc.*, **1929**, *A*, **125**, 370) for the reaction between silver and iodine: it might be expected, since the state of

iodine in the two solvents is believed to be the same, *i.e.*, simple molecules. Table II shows that the rate in diamyl ether is much less than the rates in carbon tetrachloride at the same concentration. This might be due to any of the following causes: (1) Only the free iodine molecules diffuse through the cuprous iodide film and react with the metal. (2) Both the free iodine molecules and the complex molecules diffuse through the film but only the free iodine molecules react. (3) Both the free iodine molecules and the complex may react with the copper, but the passage of the complex through the cuprous oxide layer will almost certainly be much slower, owing to its large molecular size.

FIG. 7.



Ratio between ordinates for benzene to ordinates for carbon tetrachloride.

Fig. 3 shows the rate of reaction in benzene compared with the rate in carbon tetrachloride at the same concentrations. Consider first the experiments at concentrations 0·01, 0·02, and 0·04N. The rate of reaction is less than in carbon tetrachloride and the difference increases with increase of iodine concentration. However, the rate of 0·0025N-iodine in benzene is slightly greater than the rate at the same concentration in carbon tetrachloride. If, in Fig. 3, the ordinates of the graph of the reaction in 0·04N-iodine in benzene are compared with those of the graph of 0·04N-iodine in carbon tetrachloride, a fairly constant value of the ratio is obtained; *e.g.*, at time 390, 300, 210, 150, and 60 minutes this ratio is 0·60, 0·61, 0·60, 0·61, and 0·60, respectively. This is, of course, a perfectly arbitrary method of comparing the reaction rates. The average values of this ratio for all the concentrations are plotted against concentration and given in Fig. 7, and show the effect of concentration on the difference in reaction rate in the two solvents. Above concentrations of approximately N/200 the rate in benzene is less than that in carbon tetrachloride; below N/200 it is greater. It is difficult to see any obvious explanation of this inversion.

Graphs for results at 0°, 25°, and 30° are shown in Fig. 4 and it is seen that the temperature coefficient is very small, much less than in the aqueous solutions.

Unlike the reaction in aqueous solution, in organic liquids the rate is affected by the nature of the metal surface; in general, coarseness of surface tends to increase the rate of reaction. The rate of reaction in both benzene and carbon tetrachloride is decreased by the presence of an oxide film, the degree of reduction increasing with the period of oxidation.

Measurements of the rate in carbon tetrachloride of specimens covered with a cuprous iodide film deposited from aqueous solution showed that the rate was much lower than that obtained with a clean metal surface. Conversely, the rate in aqueous solution of a copper specimen covered with a film deposited from a carbon tetrachloride solution was the same as with the new metal specimen. Clearly, the difference is not due to a difference in the structure of the film deposited from the two types of liquid, aqueous and organic.

When the kinetics of this reaction in aqueous and organic solutions are compared, interest centres round the fact that in aqueous solutions the rate is unaffected by the film, whereas in organic solutions the film appears to control the reaction. It is necessary to explain this difference, which cannot be traced, as we have seen, to differences in the structure of the films of cuprous iodide formed in the two cases. It has been stated (Part I) that in reactions in aqueous solution both solvent and solute are believed to pass through the iodide film. It is possible, however, that in organic solvents these do not enter the film but only the solute diffuses through the iodide. These films are readily wetted by water, but on the other hand, it was found that when a sheet of copper was removed from an organic solution of iodine and the surface liquid drained off the film appeared dry and the weight did not decrease with time as might be expected if the liquid were in the pores of the film and hence evaporated slowly. Attempts were made to remove a portion of a film, to support it on a small stand made from thin glass rod, and touch its upper surface with a drop of carbon tetrachloride. The spreading of the liquid on the solid did not take place rapidly, and for some time the under side of the film showed no signs of the liquid soaking through. Owing to cracks formed in the films, they always collapsed after about a minute, so little reliable evidence was obtained. Some evidence for the fact that organic solvents do not enter the iodide film is obtained from a consideration of the reaction in different organic solvents. If the reaction proceeds by the passage of iodine and solvent through the film, then it might be supposed that in using organic solvents of different viscosities different rates might be obtained. The rates of reaction in carbon tetrachloride and in chloroform, in both of which solvents all the evidence points to the iodine existing as simple molecules, are identical, whereas the viscosities of the two solvents are widely different. As shown above, the state of iodine in benzene and diamyl ether is complex and so prevents a consideration of the rates carried out in them with respect to the above; but the evidence from solutions in chloroform and in carbon tetrachloride alone suggests that the organic solvents do not themselves diffuse through the cuprous iodide film.

Adopting this theory, we have still to consider the mechanism by which the iodine molecules diffuse through the film. Three mechanisms appear to be possible: (1) The iodine might diffuse through large cracks in the film (a type of gaseous diffusion); (2) it might diffuse through small pores in the film, possibly in loose union with the cuprous iodide; (3) the diffusions might take place through atomic holes in the cuprous iodide crystal lattice.

The diffusion mechanism of (1) would depend on the vapour pressure of the iodine, which would increase rapidly with rise of temperature, and this would result in a relatively large temperature coefficient. The very small temperature coefficient observed is evidence against this. Mechanism (2), passage of iodine through pores little larger than the molecules themselves, is not impossible. If some type of attraction exists between the iodine and the cuprous iodide little energy would be required for the diffusion. The small temperature coefficient found is some evidence for this. (3) According to the theories developed by Jost and Schottburg " atomic holes " exist as lattice defects in any crystalline material, and it is possible that diffusion of iodine may take place in this manner. This theory of diffusion has, of course, attracted much attention during recent years. Like mechanism (2), this process would require little energy, and it is not possible to distinguish between (2) and (3) by a consideration of the temperature coefficient.

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212. *Deoxypentose Nucleic Acids. Part I. Preparation of the Tetrasodium Salt of the Deoxypentose Nucleic Acid of Calf Thymus.*

By J. Masson Gulland, D. O. Jordan, and C. J. Threlfall.

The preparation of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus is described by a method in which the nucleoprotein is first isolated and then decomposed; during these processes the reaction did not vary significantly from pH 7. The analytical data support the relative proportions of nucleotides indicated by titration (Gulland, Jordan, and Taylor, Part II, this vol., p. 1131).

Gulland, Barker, and Jordan (*Ann. Rev. Biochem.*, 1945, **14**, 175) have suggested that the direct isolation of nucleic acids from tissues may lead to a degraded product, and they consider that a more satisfactory procedure is to isolate and subsequently decompose the nucleoprotein. In the method which has been developed, therefore, the deoxypentose nucleoprotein of calf thymus was first isolated by making use of the remarkable difference in solubility of the nucleoprotein in sodium chloride solutions of different strengths described by Mirsky and Pollister (*Proc. Nat. Acad. Sci. U.S.*, 1942, **28**, 344; *Biol. Symposia*, 1943, **10**, 24). The deoxypentose nucleic acid was then separated from the protein by the method introduced by Sevag, Lackman, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425).

The material obtained by this preparation gave satisfactory analytical figures for carbon, hydrogen, phosphorus, and sodium, but the nitrogen value was low, being 15·4% compared with the theoretical value of 15·9% based on a polynucleotide containing the four nucleotides in equimolecular quantities. Furthermore the ratio of the purine nitrogen content to that of pyrimidine nitrogen was low, a mean value of 1·6 being obtained in place of the theoretical value of 2·0. These data may be interpreted with the aid of the results of electrometric titration (Part II, *loc. cit.*), which, whilst indicating that for every four atoms of phosphorus there is 1·0 radical of thymine and 1·0 of guanine, suggest that the amount of cytosine may be as high as 1·2 radicals and of adenine as low as 0·8 radical. Re-calculation of the theoretical nitrogen analysis on this basis gives a value of 15·5%, and the purine nitrogen/pyrimidine nitrogen ratio has the value 1·6. These data are in satisfactory agreement with the observed results. The theoretical values for carbon, hydrogen, phosphorus, and sodium are not affected appreciably by this change in the nucleotide ratio in the statistical polynucleotide.

Experimental

Isolation of the Tetrasodium Salt of the Deoxypentose Nucleic Acid of Thymus Gland.—Fresh frozen calf thymus glands (54·5 kg.) were minced and suspended in 0·9% sodium chloride (54 l.) and milled to produce a fine suspension. This suspension was centrifuged (6300 r.p.m.) and the solid material resuspended in 0·9% sodium chloride (45·5 l.) and milled and centrifuged as before. The ribonucleoproteins, together with cytoplasmic material, were obtained from the combined extracts (120 l.) by adding an equal volume of industrial methylated spirit, and the precipitated solid was washed by decantation with 50%, then 100% industrial methylated spirit, collected, and dried in a vacuum at room temperature. Yield, 2·68 kg.

The tissues, which were now free of material containing pentose, were suspended in 10% sodium chloride (214 l.) with vigorous mechanical stirring at 0°. At this stage the viscosity of the solution increased considerably (cf. Mirsky and Pollister, *loc. cit.*). After extraction at 0° for 48 hours, the insoluble material was removed by centrifuging (6300 r.p.m.) and the deoxypentose nucleoprotein precipitated from the resultant solution (pH 6·5) by the addition of an equal volume of industrial methylated spirit. The precipitated solid was washed with 70%, then 100% industrial methylated spirit and dried in a vacuum at room temperature. Yield, 1·69 kg. of a very slightly yellow fibrous solid.

The nucleoprotein (500 g.) was powdered to assist solution and dissolved in 10% sodium chloride (45·5 l.) with vigorous mechanical stirring. The solution, which was viscous, was clarified by centrifuging (6300 r.p.m.). To the clear solution was added an equal volume of a mixture of chloroform (35 parts) and amyl alcohol (10 parts), and the mixture was emulsified by rapid mechanical stirring. The emulsion was then separated by centrifuging (DeLaval, model " 500 ", disc type bowl, 5500 r.p.m.) into three parts: (i) the chloroform–amyl alcohol mixture, (ii) a solution containing the sodium salt of deoxypentose nucleic acid and nucleoprotein, (iii) a gel of protein hydrochloride and the chloroform–amyl alcohol mixture. The protein gel remained in the bowl of the centrifuge whereas the chloroform–amyl alcohol mixture and the solution of nucleic acid and nucleoprotein were discharged from separate outlets. The last mentioned solution was again emulsified with the chloroform–amyl alcohol mixture and the process repeated until no gel was formed on emulsification; this required nine emulsifications. The sodium salt of the deoxypentose nucleic acid was precipitated by the addition of an equal volume of industrial methylated spirit, washed free from chloride with 70% industrial methylated spirit, then 100% ethyl alcohol, and finally ether, and dried in a vacuum at room temperature. Yields from two 500 g. quantities of nucleoprotein were 130 g. and 150 g. of a white fibrous solid giving negative biuret and Sakaguchi tests [Found on sample dried at 110° in a vacuum over phosphoric oxide: C, 35·5, 35·5,

35·3; H, 3·68, 3·83, 3·56; N, 15·3, 15·3, 15·4; P, 9·35, 9·32, 9·32; Na, 6·9, 6·8 (gravimetric), 7·1 (colorimetric). Calc. for a large polynucleotide consisting of the tetrasodium salts of tetranucleotides containing on average 1 mol. each of guanine, adenine, cytosine, and thymine deoxypentose nucleotides, *i.e.* $(C_{39}H_{45}O_{24}N_{15}P_4Na_4)_x$: C, 35·4; H, 3·4; N, 15·9; P, 9·4; Na, 6·95. Calc. for a large polynucleotide consisting of the tetrasodium salts of tetranucleotides containing on average 1 mol. each of guanine and thymine, and 1·2 mols. of cytosine and 0·8 mol. of adenine deoxypentose nucleotides, *i.e.* $(C_{38\cdot8}H_{45}O_{24\cdot2}N_{14\cdot6}P_4Na_4)_x$: C, 35·4; H, 3·4; N, 15·5; P, 9·4; Na, 6·98%. In both cases the additional HONa atoms of the two terminal nucleotides of a straight-chain polynucleotide have been ignored, since their contribution is negligible if the size of the polynucleotide is large].

Determination of Purine Nitrogen/Pyrimidine Nitrogen Ratio.—The method used was that of precipitation of purines with silver sulphate (Schmidt and Levene, *J. Biol. Chem.*, 1938, **126**, 423). The sodium salt of deoxypentose nucleic acid (*ca.* 30 mg.) was hydrolysed by boiling under reflux with 5% sulphuric acid (7 ml.) for 1 hour. When cold, the solution was diluted to 25 ml., the total nitrogen was determined on a portion (2 ml.), and 2 ml. samples were treated with an equal volume of saturated silver sulphate. The solution containing the precipitate of the silver salts of guanine and adenine was cooled at 0° for ½ hour. The precipitate was separated by centrifuging and washed twice by stirring at 0° with a saturated solution of silver sulphate (2 ml.) followed by centrifuging. The solution was combined with the washings and analysed for pyrimidine nitrogen. The precipitate was decomposed with dilute hydrochloric acid (2 ml.), and the silver chloride removed by centrifuging and washed twice with dilute hydrochloric acid (2 ml.). The solution was combined with the washings and analysed for purine nitrogen. The purine nitrogen/pyrimidine nitrogen ratio was found to be 1·60, 1·63, 1·60, 1·58, 1·57 for five separate hydrolyses; mean, 1·60. The discrepancy between this value and the theoretical of 2 for a statistical polytetranucleotide is greater than the experimental error indicated by the Table. Nevertheless we should not have inclined to attribute undue significance to the ratio, were it not for the agreement between it, the analytical data, and the results of electrometric titration; this uniformity of trend does suggest that the purine/pyrimidine nitrogen now recorded has real meaning.

In order to confirm the accuracy of the method claimed by Schmidt and Levene (*loc. cit.*), a series of analyses of known purine and pyrimidine derivatives was performed; representative results are recorded in the Table. Determination of the purine/pyrimidine nitrogen ratio of two samples of yeast ribonucleic acid was made for comparison, the results being 1·84, 1·86; 1·84, 1·90.

Substance.	Total N, mg.	Purine N, mg.	Pyrimidine N, mg.	Recovery, %.
Guanine	10·42, 10·17, 10·38, 9·80	10·48, 10·29, 10·56, 9·70	—	100·6, 101·2, 101·7, 99·0
Adenine	10·50	10·22	—	97·3
Hypoxanthine	8·06	7·90	—	98·1
Guanosine	9·53, 8·78	9·62, 8·91	—	101·0, 101·4
Adenosine	8·49, 9·40	8·43, 9·30	—	99·3, 98·9
Thymine	1·46, 7·20	—	1·39, 7·40	94·3, 102·8
Cytidine	6·45	—	6·44	99·9
Uridine	2·98	—	2·99	100·3
Guanine * }	9·40	9·30	—	{ 98·0
Uracil * }	6·95	—	7·15	{102·9

* Mixed.

Analytical Methods.—The sodium salt of deoxypentose nucleic acid is extremely hygroscopic when dried, as in this instance, at 110°/0·1 mm. over phosphoric oxide, and special technique was required in order to minimise exposure of the dried material to atmospheric moisture. Estimations of carbon by combustion presented some difficulty owing to the occlusion of carbon by the sodium metaphosphate residue in the boat, but this problem was solved by the addition of small quantities of anhydrous potassium chlorate to the fused mass at the end of the combustion. Determinations of nitrogen were made by a modified micro-Kjeldahl technique embodying the methods of Elek and Sobotka (*J. Amer. Chem. Soc.*, 1926, **48**, 501) and Friedrich ("Die Praxis der quantitativen organischen Mikroanalyse," 1933, Deuticke, Leipzig and Vienna); of phosphorus by a modification of the method of Embden (*Z. physiol. Chem.*, 1920, **113**, 138); and of sodium either gravimetrically (as sodium sulphate after removal of phosphate as barium phosphate) or colorimetrically (Hoffman and Osgood, *J. Biol. Chem.*, 1938, **124**, 347).

It is a pleasure to acknowledge our gratitude to Boots Pure Drug Company Ltd. for carrying out the large scale operations; to the British Empire Cancer Campaign for a grant which defrayed part of the cost; and to Imperial Chemical Industries Ltd. for the loan of apparatus. We wish also to record our thanks to Mr. J. E. Still, B.Sc., for the analyses for C, H, N, and P, and to Mr. H. F. W. Taylor, B.Sc., and Mr. J. M. Creeth, B.Sc., for the sodium analyses.

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, November 2nd*, 1946.]

213. *Deoxypentose Nucleic Acids. Part II. Electrometric Titration of the Acidic and the Basic Groups of the Deoxypentose Nucleic Acid of Calf Thymus.*

By J. Masson Gulland, D. O. Jordan, and H. F. W. Taylor.

The acidic and the basic groups of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus and of barium thymate derived therefrom have been titrated electrometrically, employing hydrogen and glass electrodes. This polynucleotide is found to possess three amino-, two purine–pyrimidine enolic hydroxyl, four primary phosphoryl, and not more, and probably less, than 0·25 secondary phosphoryl dissociations for every four atoms of phosphorus. These data are consistent with a chain structure for this acid in which branching, if it occurs, is infrequent as compared with yeast ribonucleic acid. The main internucleotide bond is an ester linkage. For every four atoms of phosphorus it is found that there are 1·0 guanine, 1·0 thymine, 1·0 to 1·2 cytosine, and 1·0 to 0·8 adenine radicals.

The initial dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus obtained by titrating from pH 6·9 with acid and alkali are abnormal, being displaced from the back-titration curves. This discrepancy between the forward- and back-titration curves persists in high concentrations of neutral salt. It is concluded that the purine–pyrimidine hydroxyl groups and some of the amino-groups are blocked, most probably by a hydrogen bond between these groups. The significance of this linkage in the macromolecular structure of the tetrasodium salt of the deoxypentose nucleic acid is discussed.

The conflicting results obtained previously from investigations of the acid–base properties of thymus deoxypentose nucleic acid (Steudel, *Z. physiol. Chem.*, 1912, **77**, 497; Feulgen, *ibid.*, 1919, **104**, 189; Levene and Simms, *J. Biol. Chem.*, 1925, **65**, 519; 1926, **70**, 327; Makino, *Z. physiol. Chem.*, 1935, **232**, 229; 1935, **236**, 201; Bredereck, Köthnig, and Lehmann, *Ber.*, 1938, **71**, 2613; Bredereck and Köthnig, *ibid.*, 1939, **72**, 121; Ahlström, Euler, Fischer, Hahn, and Högberg, *Arkiv Kemi, Min. Geol.*, 1945, **20**, *A*, 1) may be ascribed to the different degrees of degradation of the samples studied (Schmidt, Pickels, and Levene, *J. Biol. Chem.*, 1939, **127**, 251; Cohen, *ibid.*, 1942, **146**, 471; Tennent and Vilbrandt, *J. Amer. Chem. Soc.*, 1943, **65**, 424; Gulland, Barker, and Jordan, *Ann. Rev. Biochem.*, 1945, **17**, 175). In all probability the least degraded specimens which have hitherto been examined were those prepared by the method of Bang (Hofmeister's " Beiträge chem. Physiol. Path.", 1903, **4**, 331) and studied conductimetrically by Hammarsten (*Biochem. Z.*, 1924, **144**, 383) and electrometrically by Jorpes (*Biochem. J.*, 1934, **28**, 2102) and Stenhagen and Teorell (*Trans. Faraday Soc.*, 1939, **35**, 743). They were found to possess four acid-dissociating groups per hypothetical tetranucleotide, having the very approximate pK_a' values of 2·4, 3·7, 4·3, and 5·2. The Hammarsten–Bang method of isolation, however, gave a product which on analysis was found to be very deficient in nitrogen and phosphorus (N, 11·97; P, 7·09%; Hammarsten, *loc. cit.*) when compared with the theoretical for the tetrasodium salt (N, 15·85; P, 9·37%). Furthermore, Hammarsten studied the free acid obtained from the sodium salt by the action of hydrochloric acid; as will be shown in this paper this treatment causes an irreversible change in that the free acid isolated from solutions more acid than pH 3·5 does not show the same acid–base properties as the sodium salt isolated at pH 7·0.

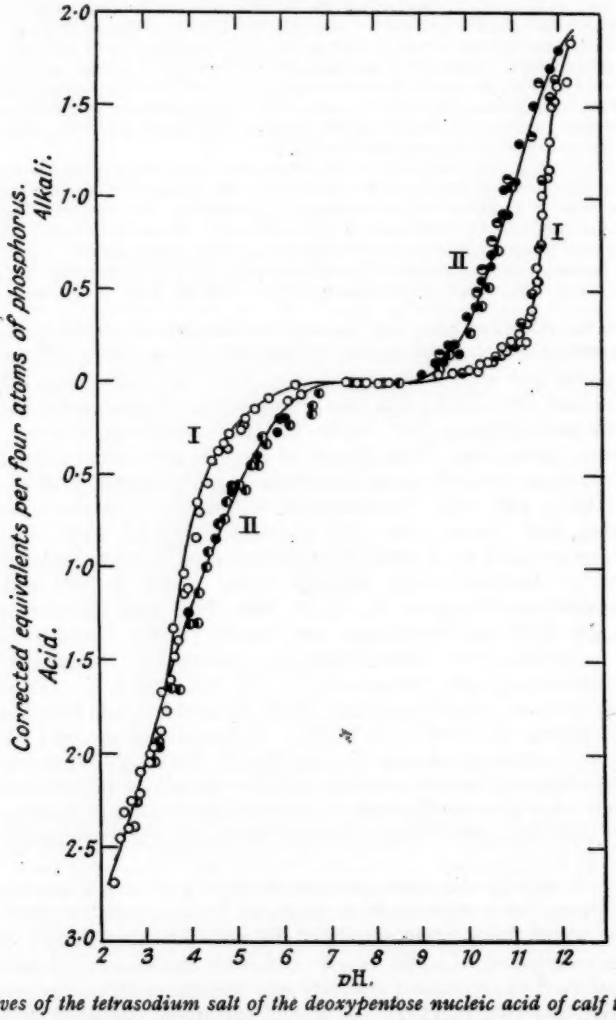
The sodium salt of calf thymus deoxypentose nucleic acid which has been studied in this investigation was isolated by a mild method (Gulland, Jordan, and Threlfall, Part I, this vol., p. 1129), throughout which the solution employed did not vary significantly from pH 7·0.* The solid was fibrous and dissolved in water to give a faintly opalescent solution, having a pH of 6·90, which exhibited marked structural viscosity and streaming birefringence (Creeth, Gulland, and Jordan, Part III, this vol., p. 1141). A second specimen, prepared by the Hammarsten–Bang procedure and supplied by Professor Caspersson through Professor Astbury in 1939, has also been studied. It was found to contain a small amount of protein which was removed by the method of Sevag, Lackman, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425), and is believed to be identical with that studied with ultracentrifuge and viscosity methods by Signer, Caspersson, and Hammarsten (*Nature*, 1938, **141**, 122) and with *X*-ray methods by Astbury and Bell (*ibid.*, p. 747).

* It is necessary to correct a point in the paper of Tennent and Vilbrandt (*J. Amer. Chem. Soc.*, 1943, **65**, 424). The sample of " Thymonucleic acid TNA2, prepared by Gulland ", referred to by these authors, was a purchased commercial sample, and the " barium thymate BT1, prepared by Gulland " was made from it by the usual method. These were given to Professor Astbury in 1939 with a warning that their purity and homogeneity was open to doubt; they were not intended for the type of investigation to which they have been put by Tennent and Vilbrandt, and in our view results obtained with them are of no value in connection with nucleic acid structure.

Results of the Present Investigation.—All electrometric titration curves have been corrected at the extremes of pH for the titration of the water by the method of Jordan and Taylor (*J.*, 1946, 994).

(i) *Titration of the sodium salt of thymus deoxypentose nucleic acid.* The titration curve of this sample is shown in Fig. 1, curve I. It will be seen that on the addition of acid or alkali to

FIG. 1.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus:

I. *Titration with acid or alkali from pH* 6·9, ○, ◒. *The smooth curve drawn through these points is calculated for* 1 *equiv. each of* pK_a' *values* 2·6, 3·5, 5·2, 10·4 and 11·4.

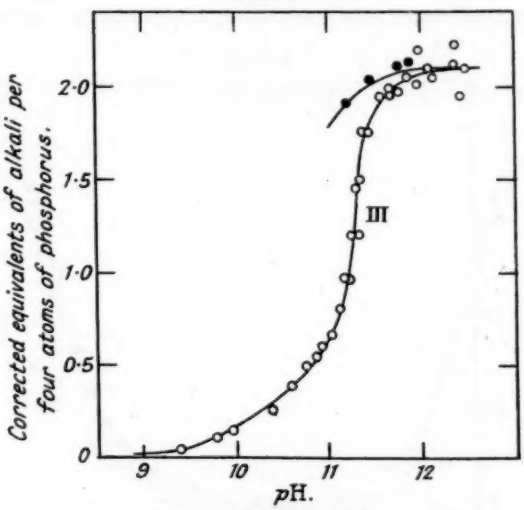
II. *Back titration with acid from pH* 12·0, ●, ◓ *and with alkali from pH* 2·5, ◐.

Points marked ◒ *and* ◓ *obtained with "Alki" glass electrode (Cambridge Instrument Co., Ltd.); all other points obtained with hydrogen electrode.*

the solution in water no groups are titrated at first between pH 5·0 and 11·0, but that outside these limits there occurs a rapid liberation of groups titrating in the ranges pH 2·0 to 6·0 and pH 9·0 to 12·0. On back titration either with acid from pH 12·0 or with alkali from pH 2·5, a curve (II) is obtained which is different from that representing the initial titration, and it is significant that the same curve (II) is obtained whether the back titration is with alkali from pH 2·5 or with acid from pH 12·0. This complete identity of the back-titration curves suggests that acid and alkali have an identical effect in liberating both sets of groups.

The back-titration curve exhibits a well-defined point of inflection in the neutral region, and shows incipient points of inflection in the regions of pH 12·0 and pH 2·0, corresponding respectively to approximately 2·0 equivalents of alkali and 3·0 equivalents of acid for each four atoms of phosphorus. There is some difficulty in interpreting electrometric titration

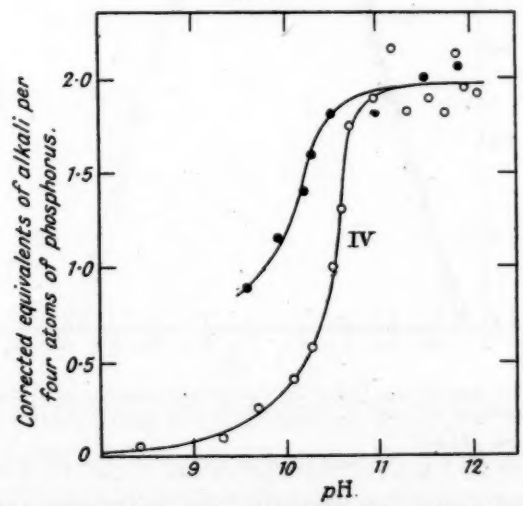
FIG. 2.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus in M*-potassium chloride.*

Titration with alkali from pH 6·9, ○ ; *back titration with acid from pH* 12·5, ●.

FIG. 3.



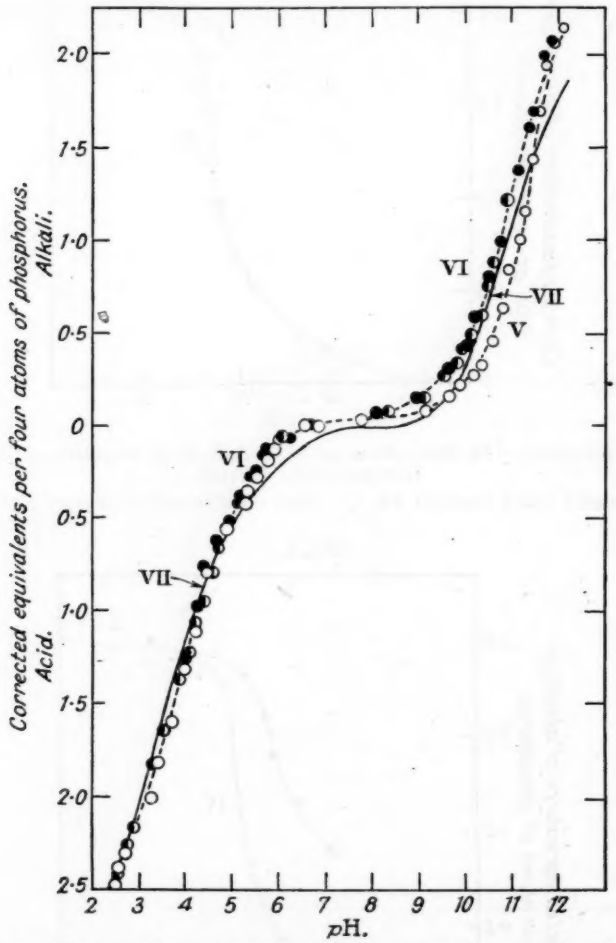
The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus in 2·5M*-guanidine sulphate.*

Titration with alkali from pH 6·9, ○ ; *back titration with acid from pH* 12·0, ●.

data above pH 11·0 and below pH 3·0 owing to the dependence of the water correction on the ionic strength (Jordan and Taylor, *loc. cit.*), which, for a polybasic substance such as nucleic acid, cannot be estimated with certainty. In obtaining the data given in Fig. 1, the assumption has been made that the acidic and basic groups contribute independently to the ionic strength. This approximation is justified by the fact that no appreciable proportion of the phosphorus

atoms carry more than one dissociating group (see below). It appeared desirable, however, to have additional confirmation of the number of groups titrating in the alkaline region, and titration of the sodium salt of thymus deoxypentose nucleic acid was therefore carried out in M-potassium chloride. The presence of the potassium chloride has the effect of masking all other contributions to the ionic strength (Cohn, Green, and Blanchard, *J. Amer. Chem. Soc.*, 1937, **59**, 509), and the water correction is obtained from a titration of M-potassium chloride. The results of this titration, which are given in Fig. 2, curve III, show conclusively that the

FIG. 4.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus after alkaline treatment followed by precipitation with alcohol at pH 7:

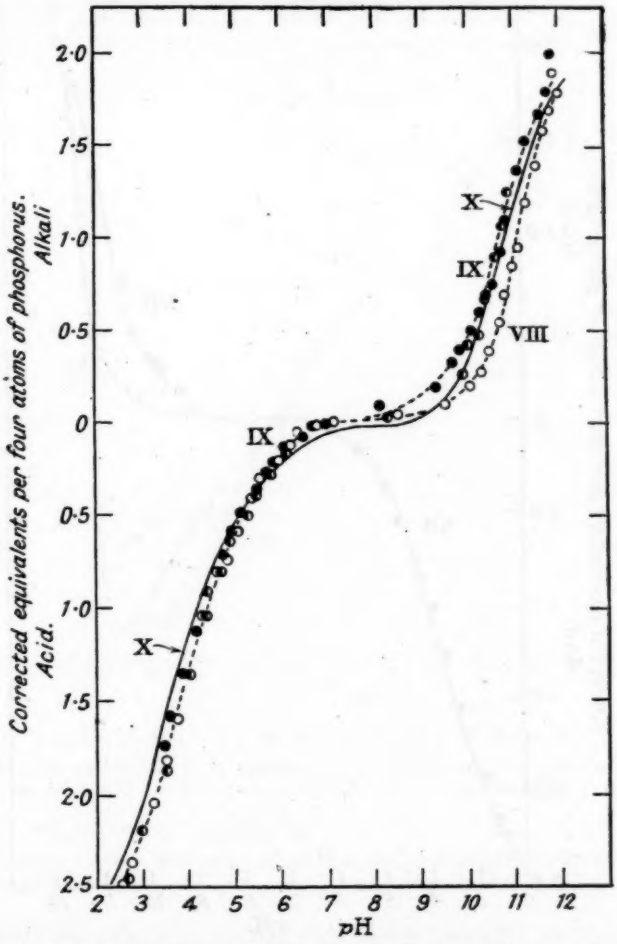
V. *Titration with alkali from pH* 6·7, ○.
VI. *Titration with acid from pH* 6·7, ○; *back titration with alkali from pH* 2·5, ◐; *back titration from pH* 12·0, ●.
VII (*full curve*). *Mean titration curve of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus from Fig.* 1.

number of groups dissociating in the range pH 8·0 to 12·0 is 2·05. Owing to the ease with which precipitation of the deoxypentose nucleic acid occurs in the presence of M-potassium chloride when acid is added, a complete back titration below pH 11·2 was not practicable; the data which have been obtained, however, are sufficient to indicate that the discrepancy between the forward- and back-titration curves described above persists in the presence of M-potassium chloride. Very similar results were obtained by titration in 2·53M-guanidine sulphate ($[C(NH_2)_3]_2SO_4$; Fig. 3, curve IV). Owing, however, to the existence of an unsteady liquid-

junction potential between this solution and the saturated potassium chloride bridge, the pH values were not very reproducible, especially in strongly alkaline solutions.

(ii) *Titration of the sodium salt of thymus deoxypentose nucleic acid precipitated with alcohol at pH 7·0 after treatment with alkali at pH 12·0, or with acid at pH 3·0.* The titration curves of an alkali-treated sample are shown in Fig. 4, curves V and VI; similar results were obtained with two other samples. The results of titration on the alkaline side of neutrality resemble those obtained with the original substance, in that a shift in the dissociation curve is observed

FIG. 5.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus after acid treatment followed by precipitation with alcohol at pH 7 :

VIII. *Titration with alkali from pH* 7·1, ○.
IX. *Titration with acid from pH* 7·1, ○ ; *back titration from pH* 2·3, ◐ ; *back titration from pH* 12·0, ●.
X (*full curve*). *Mean titration curve of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus from Fig.* 1.

on back titration, although to a somewhat smaller extent. No such effect, on the other hand, was observed on the acid side. The back-titration curves from pH 12·0 or pH 2·5 are identical, and are very similar to the curve obtained with the original substance.

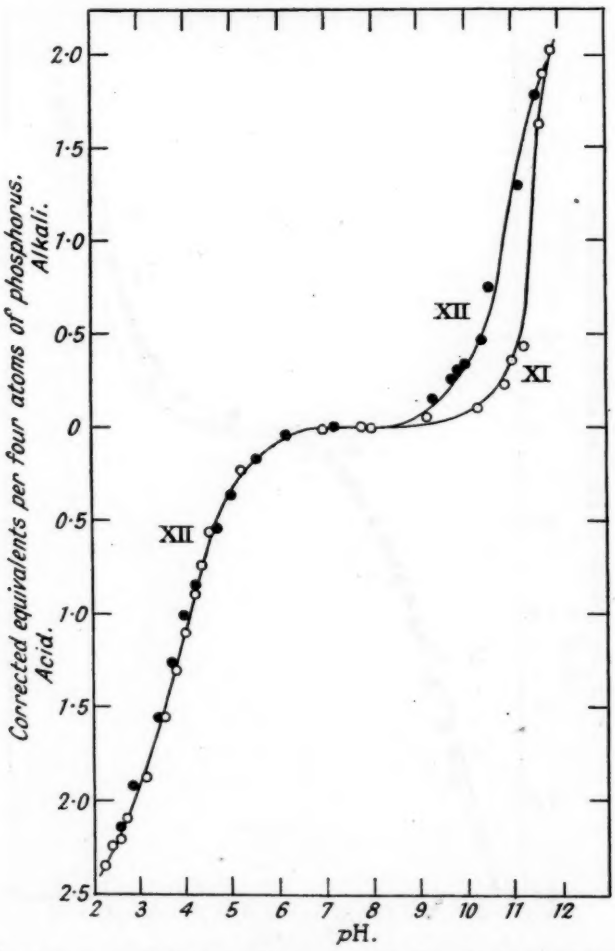
The results obtained with an acid-treated specimen (Fig. 5, curves VIII and IX) are almost identical with those described above for the alkali-treated material.

(iii) *Titration of the sodium salt of thymus deoxypentose nucleic acid supplied by Professor Caspersson.* The titration curves of this sample are shown in Fig. 6, curves XI and XII, and

are intermediate between those of the alkali- and acid-treated materials prepared by us and those of our original material. Viscosity studies (Creeth, Gulland, and Jordan, *loc. cit.*) support the view that, compared with the acid prepared by us, the sample of Caspersson exhibits different, probably less, hydrogen bonding (see below) and lower viscosity.

(iv) *Titration of the barium salt of thymic acid.* On treating thymus deoxypentose nucleic acid with dilute sulphuric acid at 80°, quantitative removal of guanine and adenine takes place (Feulgen, *Z. physiol. Chem.*, 1918, **101**, 296; Feulgen and Landmann, *ibid.*, **102**, 262; Bredereck

FIG. 6.



The dissociation curves of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus supplied by Professor Caspersson :

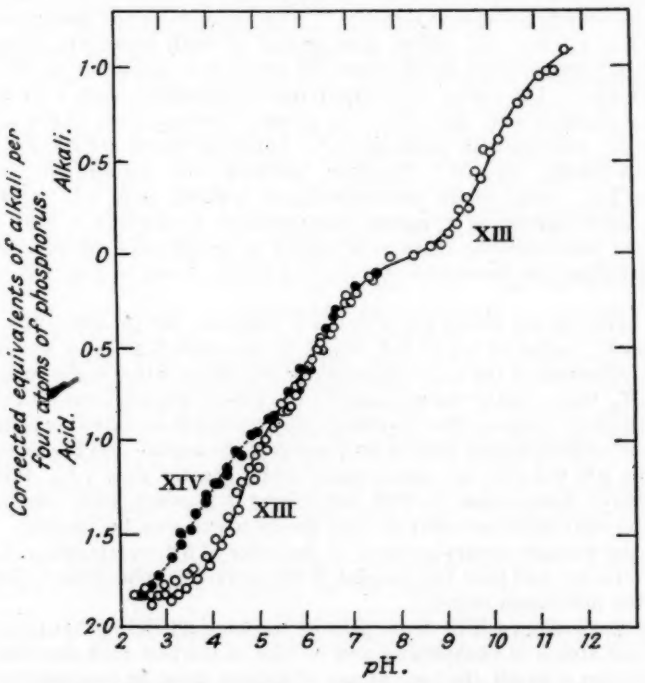
XI. *Titration with alkali from pH* 7·8, ○.
XII. *Titration with acid from pH* 7·8, ○ ; *back titration from pH* 11·8, ●.

and Müller, *Ber.*, 1939, **72**, 115); the resulting thymic acid is isolated as its barium salt. The empirical formula weight of this substance is defined, for convenience, as the amount containing 4 g.-atoms of phosphorus, and the values obtained from the phosphorus contents of the two preparations studied were 1310 and 1315. The electrometric titration curve calculated on the basis of these formula weights is shown in Fig. 7, curve XIII, well-marked points of inflection being observed at pH 2·5, 8·0 and 11·5 after the neutralisation of 1·85 and 1·0 equivalents respectively. A titration has also been carried out in the presence of formaldehyde in order to ascertain what proportion of the more acidic dissociation represents that of an amino-group (curve XIV).

Discussion.—(i) *The nature of the acidic and the basic groups of deoxypentose nucleic acid.* The problem of the initial structure of deoxypentose nucleic acid before alkali or acid treatment will be considered in section (ii) of this discussion, and in this section the back-titration curve (Fig. 1, curve II) only will be treated.

Owing to the fact that the deoxyribonucleotides have not yet been isolated in quantities sufficient to permit an investigation by electrometric methods, it is necessary to refer to dissociation-constant data of the ribonucleotides in order to interpret this curve. This procedure is to some extent justified by the fact that the pK_a' values of the amino-groups of adenylic

FIG. 7.



The dissociation curves of the barium salt of thymic acid :

XIII. *Titrations with acid and alkali from approximately pH 7,* ○. *The smooth curve drawn through these points is calculated for* 1·1 *equivs. of* pK_a' 4·6, 0·75 *equiv. of* pK_a' 6·5, *and* 1·0 *equiv. of* pK_a' 10·0.

XIV. *Titration in* 1·875% *formaldehyde solution,* ●.

(*The zero of equivalents is fixed arbitrarily at pH* 8·4, *the titrations being carried out on two samples of slightly different barium content.*)

and cytidylic acids do not differ very greatly from those of adenine and cytosine respectively, as shown by the following data :

Adenine	4·15	Adenylic acid	3·70 [1]
Cytosine	4·60 [1]	Cytidylic acid	4·24 [1]

[1] Data of Levene and Simms (*loc. cit.*).

It is not expected, therefore, that replacement of *d*-ribose by deoxypentose would give rise to any considerable change in the pK_a' values.

There has been some confusion in the literature between the pK_a' values assigned to the amino- and the primary phosphoryl dissociations of nucleic acids. Levene and Simms (*loc. cit.*) considered the groups dissociating in the range pH 2·0 to 6·0 to be the amino-groups, whereas Hammarsten (*loc. cit.*) and Fletcher, Gulland, and Jordan (*J.*, 1944, 33) considered them to be the primary phosphoryl dissociations. Consideration of the pK_a' values for the

nucleosides and sugar phosphates (given below) in the light of the modern theory of zwitterions points conclusively to the former view being correct.*

Adenosine	3·45	(Levene and Simms, *loc. cit.*).
Sugar phosphates...	pK_{a_1}', 0·8 to 1·1; pK_{a_2}', 6·0 to 6·5	(Kumler and Eiler, *J. Amer. Chem. Soc.*, **1943, 65**, 2355).
Adenylic acid	pK_{a_1}', 0·89; pK_{a_2}', 3·70; pK_{a_3}', 6·01	(Levene and Simms, *loc. cit.*).

The pK_{a_1}' value of adenylic acid is clearly that of a primary phosphoryl dissociation, the pK_{a_2}' an amino-dissociation, and the pK_{a_3}' a secondary phosphoryl dissociation. At the isoelectric point, therefore, nucleic acids will exist almost entirely in the zwitterionic form.

The dissociations which will be titrated in the range pH 2·5 to 8·0 are therefore those of the amino- and the secondary phosphoryl groups. Examination of the lower portion of the back-titration curve (Fig. 1, curve II) shows that groups of both types are present, although the amount of secondary phosphoryl dissociation for every four atoms of phosphorus is relatively very small (see below). The curve is in approximate agreement with a theoretical curve constructed for 1·0 equivalent each, for every four atoms of phosphorus, of the amino-dissociations of guanylic, adenylic, and cytidylic acids, the pK_a' values of which are 2·3, 3·7, and 4·24 respectively (Levene and Simms, *loc. cit.*; Fletcher, Gulland, and Jordan, *loc. cit.*). It appears, however, that the pK_a' value of the amino-group of cytidylic acid (*viz.*, 4·24) which has been assumed for the amino-group of cytosine deoxypentose nucleotide is low, and much better agreement with the experimental curve is obtained by employing the pK_a' values of 2·5, 3·5, and 5·2 for constructing the theoretical curve; the curve shown in Fig. 1 is calculated on this basis.

The titration curve in the range pH 5·5 to 7·5 indicates the presence of a small amount of a group having a pK_a' value of 6·0 to 6·5, which is considered to be a secondary phosphoryl group. The determination of the exact quantity of this dissociation is dependent upon a precise knowledge of its pK_a' value and of the amounts of the amino-dissociations and their pK_a' values, but using 6·5 for the pK_a' value of the secondary phosphoryl dissociation, which is that observed for thymic acid, and assuming that there is no overlap of the amino- and the secondary phosphoryl dissociations above pH 6·5 (*i.e.*, no amino-dissociation greater than pK_a' 4·5), the amount of secondary phosphoryl dissociation is 0·25 equivalent for every four atoms of phosphorus. This represents the maximum amount of this group which can be present. Since, however, the pK_a' value of the weakest amino-group is of the order of 5·2, overlapping of the dissociations above pH 6·5 must occur, and thus the amount of the secondary phosphoryl dissociation present will be less than the maximum value.

The analysis of the sodium salt of deoxypentose nucleic acid shows that there are four sodium atoms for every four atoms of phosphorus, and in view of the fact that the amount of secondary phosphoryl dissociation is small, the four atoms of sodium must be combined largely or entirely with four primary phosphoryl dissociations. The deoxypentose nucleic acid of calf thymus differs in this respect markedly from the ribonucleic acids of yeast (Fletcher, Gulland, and Jordan, *loc. cit.*) and of *Calliphora erythrocephela* (Khouvine and Grégoire, *Bull. Soc. Chim. biol.*, **1944, 16**, 421), both of which show 1·0 equivalent of secondary phosphoryl dissociation (on correction for the phosphorus analysis) for every four atoms of phosphorus, and it cannot therefore possess the branched chain structure postulated for yeast ribonucleic acid by Fletcher, Gulland, and Jordan (*loc. cit.*). The data recorded are, however, consistent with the view that the thymus deoxypentose nucleic acid of calf thymus has a long, unbranched chain structure (Signer, Caspersson, and Hammersten, *loc. cit.*; Astbury and Bell, *loc. cit.*).

The groups titrating in the range pH 8·0 to 12·0 are considered to be the purine–pyrimidine hydroxyl groups of thymine and guanine deoxypentosides, and the upper part of the back-titration curve is in agreement with a theoretical curve constructed for 1·0 equivalent each of pK_a' values 10·4 and 11·4. The corresponding pK_a' value for thymine is 9·94 (Levene, Bass, and Simms, *J. Biol. Chem.*, **1926, 70**, 229; and confirmed by us) and for guanylic acid, 9·36 (Levene and Simms, *loc. cit.*), which, although of the same order of magnitude as the upper dissociations of deoxypentose nucleic acid, are nevertheless appreciably lower. The same effect is seen to a lesser extent in yeast ribonucleic acid which shows 2·0 dissociations of pK_a' 10·2 as compared with 9·36 for guanylic acid and 9·43 for uridylic acid (Levene and Simms, *loc. cit.*; Fletcher, Gulland, and Jordan, *loc. cit.*). The reason for this discrepancy is not clear,

* Acceptance of this view does not alter the main conclusions of Fletcher, Gulland, and Jordan about the structure of yeast ribonucleic acid, except that the triply-bound phosphoryl group is not necessarily that of uridylic acid.

especially in view of the better agreement which exists between the pK_a' values for the amino-dissociations of the ribonucleotides and of a yeast ribonucleic acid. It may, however, be related to the degree of polymerisation of the nucleic acid since it is not observed in thymic acid, which is considered to have a low molecular weight (see below).

The data given in Fig. 2, curve III, show that, other than the purine–pyrimidine hydroxyl groups, there are no dissociating groups titrating with alkali which have a pK_a' value in water less than at least 13·5. This confirms the absence of free sugar hydroxyl groups in this sample, since the pK_a' values of the primary hydroxyl dissociations of many sugars are in the region of 12·5 (Hirsch and Schlags, *Z. physikal. Chem.*, 1929, **141**, *A*, 387; Stearn, *J. Physical Chem.*, 1931, **35**, 2226; Urban and Shaffer, *J. Biol. Chem.*, 1932, **94**, 697; Urban and Williams, *ibid.*, 1933, **100**, 237), and suggests that no other sugar than a deoxypentose is present in any appreciable quantity in this sample of deoxypentose nucleic acid of thymus. Furthermore, taken in conjunction with the presence of one primary phosphoryl dissociation for every atom of phosphorus, the guanine, adenine, and cytosine dissociations and the guanine and thymine hydroxyl dissociations, this fact supports the view that the internucleotide bond is an ester linkage between the phosphoryl groups and the two hydroxyl groups of the sugar which are not involved in the glycosidic ring structure. Other types of linking may, however, exist in the nucleic acid, but the sensitivity of the titration method precludes the occurrence of such other linkages to a greater extent than one for every ten to twenty nucleotides.

The titration of thymic acid, taken in conjunction with the preceding data for deoxypentose nucleic acid, supplies information concerning the proportions of the four bases guanine, adenine, cytosine, and thymine present in this sample of nucleic acid. The titration curve for thymic acid (Fig. 7) shows 1·0 dissociation per four atoms of phosphorus in the pH range 8·0 to 12·0; this group can only be the enolic hydroxyl group of thymine. The 2·0 dissociations therefore observed in this pH range for deoxypentose nucleic acid (see above) must indicate the presence of one molecule each of thymine and guanine for every four atoms of phosphorus. It is not possible to determine with certainty the relative proportions of cytosine and adenine from the titration data of the sodium salt of deoxypentose nucleic acid, although the total amount of these groups is approximately 2·0. Thymic acid, however, possesses for every four atoms of phosphorus 1·0 to 1·2 dissociations of pK_a' 4·5 which must be the amino-dissociation of cytosine, and thus it is probable that the ratio of cytosine to adenine in the deoxypentose nucleic acid is as 1·0—1·2 is to 1·0—0·8.

The presence in barium thymate of 0·75 equivalent of a secondary phosphoryl dissociation for every four atoms of phosphorus suggests, on the basis of the straight-chain structure for deoxypentose nucleic acid, that the average number of nucleotides per molecule of thymic acid is approximately 5, and thus that the average molecular weight of the free acid is of the order of 1200.

(ii) *The macromolecular structure of deoxypentose nucleic acid.* As is shown in Fig. 1, the amino- and the enolic hydroxyl groups of thymus deoxypentose nucleic acid are partly or completely blocked until the material has been treated with acid or alkali; an irreversible change then takes place with the accompanying liberation of titratable groups. The release of the groups on treatment with alkali takes place sharply in the neighbourhood of pH 11·5, but less sharply in the range pH 3·5 to 4·5 on treatment with acid. In both cases equilibrium is established almost instantaneously, and the liberation of groups is accompanied by a marked fall in the viscosity and a disappearance of streaming birefringence (Hammarsten, *loc. cit.*; Vilbrandt and Tennent, *J. Amer. Chem. Soc.*, 1943, **65**, 1806; Creeth, Gulland, and Jordan, *loc. cit.*).

The decrease in viscosity brought about by the addition of acid or alkali was considered by Vilbrandt and Tennent (*loc. cit.*) to be caused by a depolymerisation which was slowly reversed when the solution was returned to neutrality. Our results show that such a depolymerisation cannot involve the rupture of the internucleotide ester linkages since no increase of secondary phosphoryl dissociation is observed in the back-titration curve. The complete identity of the back-titration curves from pH 2·5 and pH 12·0 strongly suggests that acid and alkali have the same effect in liberating the amino- and the hydroxyl groups. Two possibilities may be considered to explain this behaviour. It could be caused by easily hydrolysed radicals, hitherto unidentified in the breakdown products of the nucleic acid, which either substitute in the amino- and the hydroxyl groups separately or form a bridge between them. There are, however, certain limitations in the type of radical which could be involved; first, it could not contain groups which are titrated in the pH range examined in this investigation, since the back-titration curve shows no liberation of such groups and is moreover almost identical with the titration curve of the acid or alkali treated samples (Figs. 4 and 5), and secondly, the stability

to acid and alkali of the links involving the amino- and the hydroxyl groups would have to be very similar. In our opinion these restrictions make the preceding explanation of the observed behaviour improbable, and a simpler and preferable explanation is that in which the amino- and the hydroxyl groups are linked by hydrogen bonds. Bonding of this type has frequently been suggested as being important in protein structure, and our observations on the behaviour of deoxypentose nucleic acid resemble in some respects those recorded for egg albumen (Cannan, Kibrick, and Palmer, *Ann. N.Y. Acad. Sci.*, **1941**, **41**, 243; Crammer and Neuberger, *Biochem. J.*, **1943**, **37**, 302), which have been interpreted by postulating a hydrogen bond between a phenolic hydroxyl group and a carboxylate ion. Although it is undesirable at the present stage to speculate too far as to the macromolecular structure of deoxypentose nucleic acid, a hydrogen bond between an amino-group and either the $-NH-$ group or the enolic $-C(OH)-$ group of an adjacent guanine or thymine radical could explain satisfactorily our experimental results. The large number of such bonds which are possible, the maximum number being two for every four atoms of phosphorus, would give a degree of stability to the untreated deoxypentose nucleic acid, and in order to degrade the nucleic acid it might be necessary to break many of the hydrogen bonds simultaneously. Such a process would lead to an abnormal titration curve of the type shown in Fig. 1. It is not possible on the basis of these data to decide whether the hydrogen bonds unite nucleotides in the same, or in different chains; this aspect is considered in the light of viscosity and streaming birefringence by Creeth, Gulland, and Jordan (*loc. cit.*).

The increase in viscosity observed at approximately pH 7 when a solution of the nucleic acid was adjusted to that value after treatment with acid or alkali (Vilbrandt and Tennent, *loc. cit.*; Creeth, Gulland, and Jordan, *loc. cit.*) does not involve the blocking of the amino- and the enolic hydroxyl groups, since the titration curves obtained were identical with the back-titration curve shown in Fig. 1 whether the solution was titrated immediately or was allowed to remain at approximately pH 7 for 96 hours in the absence of atmospheric oxygen. During this period the viscosity had risen to a value of the same order as that observed with the original acid (Creeth, Gulland, and Jordan, *loc. cit.*).

A different behaviour was observed in samples which had been precipitated by alcohol at pH 7 after acid or alkaline treatment. Some blocking of the enolic hydroxyl groups occurred (Figs. 4 and 5), but to a much smaller extent than that found with the original material, and the properties of the precipitated material appeared to be independent of the viscosity changes, since very similar titration curves were obtained whether the product was precipitated immediately or after 96 hours. Precipitation would thus seem to be the important factor. There is no evidence from titration data that precipitation effects blocking of the amino-groups.

Greenstein and Jenrette (*J. Nat. Cancer. Inst.*, **1940**, **1**, 77; *Cold Spring Harbor Symp. Quant. Biol.*, **1941**, **9**, 236) have postulated on the evidence of viscosity measurements that reversible depolymerisation of thymus deoxypentose nucleic acid takes place on the addition of neutral salts. Titration of the sodium salt of thymus deoxypentose nucleic acid in M-potassium chloride (Fig. 2) and in 2·53 molar guanidine sulphate (Fig. 3) showed that the changes in viscosity which occur bear no relation to the irreversible change which takes place on treatment with acid or alkali, since the discrepancy between the forward- and back-titration curves was still present in these salt solutions. The lowering of the viscosity by the addition of salt must therefore involve a different type of physico-chemical change to that occurring on treatment with acid or alkali.

Experimental.

Apparatus.—The electrometric titrations were carried out according to the method described by Fletcher, Gulland, and Jordan (*loc. cit.*), and the titration curves were corrected for the titration of water at the extremes of pH by the method of Jordan and Taylor (*loc. cit.*). The solutions for titration contained 100 to 200 mg. of the samples in 20 ml. of water.

Preparation of Alkali-treated Samples of the Sodium Salt of Thymus Deoxypentose Nucleic Acid.—To a solution of sodium salt of deoxypentose nucleic acid (2 g.) in water (100 ml.), 0·5N-sodium hydroxide (25 ml.) was added with mechanical stirring. The solution then had a reaction of pH 12·30. 0·5N-Hydrochloric acid (24 ml.) diluted with water (51 ml.) was added slowly with rapid stirring to avoid precipitation. The pH was finally adjusted to 7·0. The solution was added immediately or at the time required to ethyl alcohol (750 ml.). The white granular precipitate (1·6 g.) was collected, washed with alcohol, and dried in a vacuum over phosphoric oxide.

Preparation of Acid-treated Samples of the Sodium Salt of Thymus Deoxypentose Nucleic Acid.—To a solution of the sodium salt of deoxypentose nucleic acid (2 g.) in water (150 ml.), 0·08N-hydrochloric acid (50 ml.) was added slowly with constant stirring, the final reaction being pH 3·1. 0·195N-Sodium hydroxide (24 ml.) was added slowly with stirring, and the reaction adjusted to pH 7·1 with dilute hydrochloric acid. The solution was added immediately or later as required to ethyl alcohol (750 ml.).

The white granular precipitate (1·6 g.) was collected, washed with alcohol, and dried in a vacuum over phosphoric oxide.

Preparation of Barium Thymate.—A solution of the sodium salt of thymus deoxypentose nucleic acid (15 g.) in water (400 ml.) was warmed to 80° and mixed with 10% sulphuric acid (30 ml.) at the same temperature. A white solid formed and redissolved in 5 minutes. The solution was maintained at 80° for 30 minutes. Silver sulphate (5 g.) was added and the suspension shaken for 1 hour, cooled in water and then to 0°, and mixed with a solution of barium acetate (20 g.) and barium chloride (5 g.) in water (30 ml.). Next day the supernatant was decanted, and the solid collected by centrifuge and washed repeatedly with 90% alcohol and then with 100% alcohol and ether. The product (4·6 g.) was dried in a vacuum over phosphoric oxide.

Analyses.—All samples were dried at 110° in a vacuum over phosphoric oxide. Details of the analytical methods are given in Part I (*loc. cit.*). Sodium salt of deoxypentose nucleic acid of calf thymus prepared by Professor Caspersson and deproteinised by us (see text), found: C, 35·5; H, 4·14; N, 15·4; P, 9·4; Na, 7·2 (colorimetric)%. Alkali-treated sodium salt of deoxypentose nucleic acid of calf thymus (respective values for three preparations), found: C, 35·3, 35·7, 36·1; H, 3·62, 3·83, 3·79; N, 15·4, 15·6, 15·5; P, 9·30, 9·63, 9·58; Na, —, 6·42, 6·28 (gravimetric) %. Acid-treated sodium salt of deoxypentose nucleic acid of calf thymus, found: C, 35·9; H, 3·76; N, 15·8; P, 9·41; Na, 6·33 (gravimetric) %. Calc. for a large polynucleotide consisting of the tetrasodium salts of tetranucleotides containing on average 1 mol. each of guanine, adenine, cytosine, and thymine deoxypentose nucleotides, *i.e.* $(C_{39}H_{45}O_{24}N_{15}P_4Na_4)_x$, the additional HONa of the terminal groups being ignored: C, 35·4; H, 3·4; N, 15·9; P, 9·4; Na, 6·95%. Calc. for a large polynucleotide consisting of the tetrasodium salts of tetranucleotides containing on average 1 mol. each of guanine and thymine, and 1·2 mols. of cytosine and 0·8 mol. of adenine deoxypentose nucleotides, *i.e.* $(C_{38\cdot8}H_{45}O_{24\cdot2}N_{14\cdot6}P_4Na_4)_x$, the additional HONa of the terminal groups being ignored: C, 35·4; H, 3·4; N, 15·5; P, 9·4; Na, 6·98%.

Barium thymate (respective values for two preparations), found: C, 27·1, —; H, 3·46, —; N, 5·44, 5·53; P, 9·47, 9·44; Ba, 23·3, 23·1%. Calc. for a molecule containing four atoms of phosphorus, 1·2 mols. of cytosine, 1·0 mol. of thymine, 2·22 atoms of barium and a terminal OH group to every five atoms of phosphorus, *i.e.*, $C_{39\cdot4}H_{40\cdot7}O_{23\cdot8}N_{5\cdot6}P_4Ba_{2\cdot22}$: C, 26·9; H, 3·10; N, 5·96; P, 9·44; Ba, 23·2%. Calc. for a molecule containing four atoms of phosphorus, 1·0 mol. each of cytosine, and thymine, 2·22 atoms of barium, and a terminal OH group to every five atoms of phosphorus, *i.e.*, $C_{39}H_{40\cdot1}O_{23\cdot6}N_5P_4Ba_{2\cdot22}$: C, 26·8; H, 3·08; N, 5·37; P, 9·56; Ba, 23·4%.

It is a pleasure to record our thanks to Imperial Chemical Industries Ltd. for the loan of apparatus; to Professor W. T. Astbury, F.R.S., for the gift of the sample prepared by Professor Caspersson; to Mr. J. M. Creeth, B.Sc., for preparing two of the alkali-treated samples, for preliminary work on the acid treated material, and for some of the sodium analyses; to Mr. C. J. Threlfall, B.Sc., for preparing the samples of barium thymate; and to Mr. J. E. Still, B.Sc., and Mr. D. S. R. Cameron for the microanalyses.

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, November 2nd*, 1946.]

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214. *Deoxypentose Nucleic Acids. Part III. Viscosity and Streaming Birefringence of Solutions of the Sodium Salt of the Deoxypentose Nucleic Acid of Calf Thymus.*

By J. M. CREETH, J. MASSON GULLAND, and D. O. JORDAN.

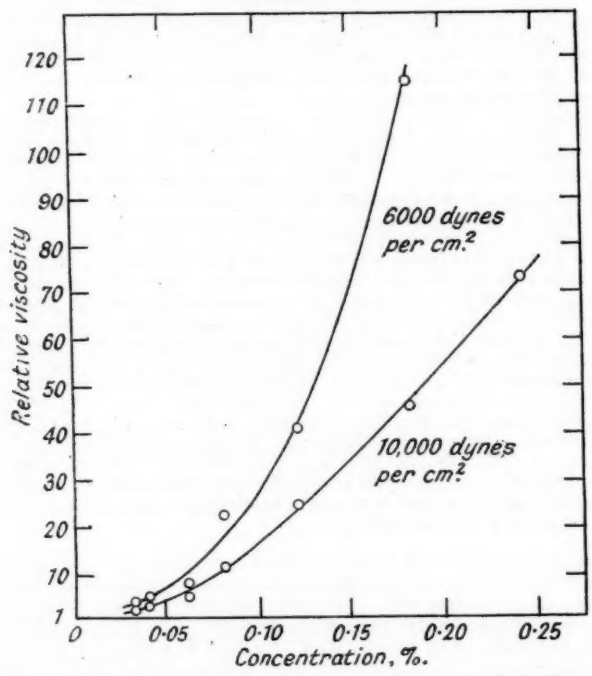
The high viscosity and marked streaming birefringence of solutions of the tetrasodium salt of deoxypentose nucleic acid of calf thymus are found to remain constant between pH 5·6 and 10·9. Outside these critical limits the viscosity falls to a very low value and the streaming birefringence disappears, but they increase again if the pH is readjusted to 7·0. The critical pH values are coincident with those at which a liberation of amino- and enolic hydroxyl groups has been observed (Gulland, Jordan, and Taylor, Part II, this vol., p. 1131) and it is considered that the two phenomena are related and are due to the fission of the hydrogen bonds postulated as linking the purine–pyrimidine hydroxyl groups and some of the amino-groups. The present data do not show whether bonding of neighbouring polynucleotide chains or of nucleotides in the same chain is involved.

The viscosities of solutions of the tetrasodium salt of deoxypentose nucleic acid of calf thymus were reduced considerably by low concentrations of neutral salt, increase of the concentration above 0·01M having relatively only a small effect on the viscosity.

THE high viscosity exhibited by aqueous solutions of the sodium salt of thymus deoxypentose nucleic acid at pH 7·0 has been shown to decrease with the addition of acid and alkali (Jones and Austrian, *J. Biol. Chem.*, 1907, **3**, 1; Jones, *ibid.*, 1908, **5**, 1; Hammarsten, *Biochem. Z.*, 1924, **144**, 383; Vilbrandt and Tennent, *J. Amer. Chem. Soc.*, 1943, **65**, 1806) and with the addition of neutral salts (Greenstein and Jenrette, *J. Nat. Cancer Inst.*, 1940, **1**, 77; *Cold Spring Harbor Symp. Quant. Biol.*, 1941, **9**, 236). A mechanism involving depolymerisation has been ascribed to both these processes (Greenstein and Jenrette, *loc. cit.*; Vilbrandt and Tennent, *loc. cit.*). In view of the observations (Gulland, Jordan, and Taylor, Part II, *loc. cit.*) that

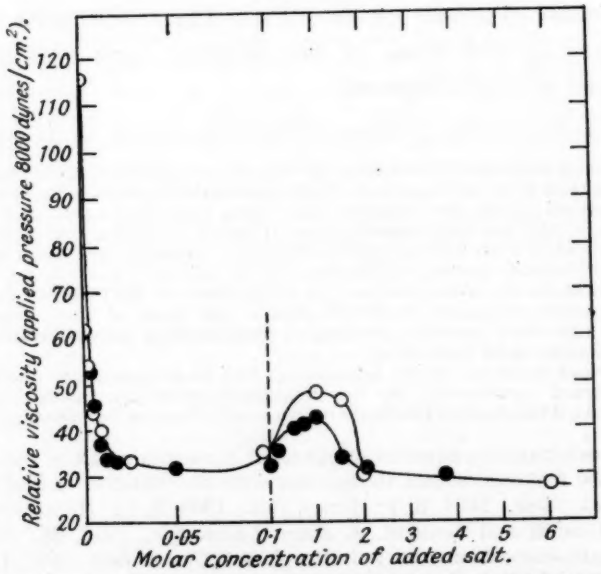
treatment with acid or alkali of solutions of the sodium salt of thymus deoxypentose nucleic acid prepared by Gulland, Jordan, and Threlfall (Part I, this vol., p. 1129) leads to the liberation

FIG. 1.



The variation of the viscosity of solutions of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus with concentration at two different pressures.

FIG. 2.



The variation of the viscosity of solutions of the tetrasodium salt of the deoxypentose nucleic acid of calf thymus with concentration of added salt.

Sodium chloride ●; guanidine chloride ○.

of titratable groups, whereas the addition of neutral salts does not, an investigation of the viscosity of solutions of this preparation of this nucleic acid appeared desirable.

Results of this Investigation.—The viscosity of aqueous solutions of this preparation of the sodium salt of thymus deoxypentose nucleic acid increased considerably with rise of concentration (Fig. 1), and the viscosity of a 0·5% solution could not be measured in the capillary viscometers used in this investigation. At all concentrations studied the viscosity varied with the applied pressure, thus being abnormal or structural in character.

The magnitude of the relative viscosity was very much greater than that recorded for other preparations of the sodium salt of this nucleic acid. Thus, the relative viscosity of our material at pH 7·0 in 0·243% solution at 25°, measured in a capillary viscometer at 8000 dynes/cm.^{2}, was 116, whereas from measurements with the sodium salt prepared by the method of Bang (Hofmeister's " Beiträge Chem. Physiol. Path.", 1903, **4**, 331) and Hammarsten (*loc. cit.*), Vilbrandt and Tennent (*loc. cit.*) record 5·7 for a 0·3% solution at 25° measured in an Ostwald viscometer, and Greenstein and Jenrette (*loc. cit.*) give 5·53, a limiting value at high pressures, for a 0·25% solution at 25° measured in a capillary viscometer.

The addition of sodium chloride or guanidine chloride (the guanidinium ion being specified as most effective by Greenstein and Jenrette) lowered very considerably the relative viscosities of solutions of the sodium salt of thymus deoxypentose nucleic acid (Fig. 2). The viscosity fell rapidly at first as the salt concentration was increased, reaching a critical value at about 0·01M with both sodium chloride and guanidine chloride. On increasing the concentration above the critical value only comparatively small changes in viscosity occurred; a rise to a slight peak and subsequent fall were observed at approximately 1M, a result which may be compared with that observed by Needham, Kleinzeller, Miall, Dainty, Needham, and Lawrence (*Nature*, 1942, **150**, 46) for the action of neutral salts on the viscosity of solutions of myosin.

The variation of the viscosity with the pH of the solution is shown in Fig. 3; the ionic strength was maintained at 0·01 throughout. The relative viscosity remained constant as the pH was varied from 5·6 to 10·9, but outside these limits it fell rapidly, and at pH 12·08 and at pH 3·38 the viscosity of the solutions no longer varied with the applied pressure. These results are not in agreement with the data recorded by Vilbrandt and Tennent (*loc. cit.*) who observed a maximum in the relative viscosity at pH 7·0 and a gradual reduction of the relative viscosity as the pH was changed in either direction from neutrality. The results of these authors resemble those obtained by us with samples of the original sodium salt of thymus deoxypentose nucleic acid which had been treated with alkali at pH 12·5 or with acid at pH 3·5 and then precipitated by the addition of ethyl alcohol at pH 7·0 (Fig. 3). Our results with the acid- or alkali-treated material also closely resemble those obtained with a sample of the sodium salt supplied by Professor Caspersson through Professor Astbury in 1939, and prepared by the Hammarsten–Bang procedure.

The data for the streaming birefringence of solutions of the sodium salt of thymus deoxypentose nucleic acid are recorded in the table, and followed closely the changes in viscosity. In agreement with the experimental results of Greenstein and Jenrette (*J. Nat. Cancer Inst.*, 1940, **1**, 77, Table 2) and the conclusions of Snellmann and Widström (*Arkiv Kemi, Min. Geol.*, 1945, **19**, *A*, No. 31) solutions of our deoxypentose nucleic acid showed considerable streaming birefringence in the presence of a high concentration (4M) of neutral salt (see table).

Variation with pH (ionic strength maintained at 0·01 throughout) and with concentration of sodium chloride of the streaming birefringence of 0·243% solution of the sodium salt of thymus deoxypentose nucleic acid.

pH	3·7	4·0 to 4·3	4·3 to 5·0	5·0 to 10·0	10·0 to 10·7	10·9 to 11·6	12·0
Streaming birefringence (relative values on arbitrary scale)	0	1	2	3	2	1	0

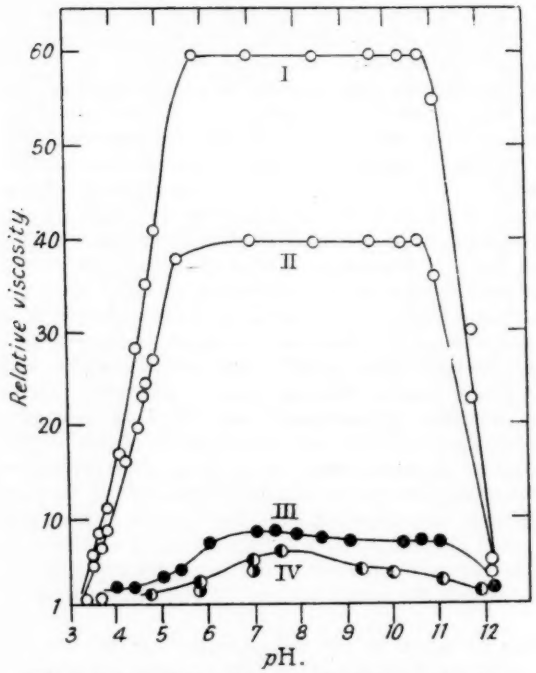
Original nucleic acid, in water at pH 6·9, 4; in 4M-sodium chloride, 2.

The action of acid and alkali in reducing the viscosity of solutions of the sodium salt of thymus deoxypentose nucleic acid has been shown by Vilbrandt and Tennent (*loc. cit.*) to be to some extent reversible if the solutions are returned to pH 7·0. We have confirmed this result, but have observed that the regain of high viscosity after acid treatment is different from that which occurs after alkaline treatment. When a 0·243% solution was left at pH 12·5 for 15 minutes and then returned to pH 7·0, the viscosity increased steadily with time (Fig. 4) and

moreover regained its structural character; after 91 hours the relative viscosity had increased to a value of the same order as that of the original acid, but the variation with applied pressure was somewhat different, the viscosity being lower at high pressures and higher at low pressures (Fig. 4). With concentrations of the sodium salt of deoxypentose nucleic acid up to 0·5% there was no appreciable increase in the viscosity at pH 7·0 after treatment at pH 3·5 for 15 minutes, but a 1·0% solution after such treatment gelled on standing for 12 hours.

When the products of alkali- or acid-treatment were precipitated at pH 7·0 by the addition of ethyl alcohol, isolated, dried, and redissolved in water, they showed only a slight increase in viscosity with lapse of time. A marked difference exists, therefore, between the behaviour of precipitated and non-precipitated material after alkali- or acid-treatment.

FIG. 3.



The variation of the viscosity of solutions of various specimens of deoxypentose nucleic acid.

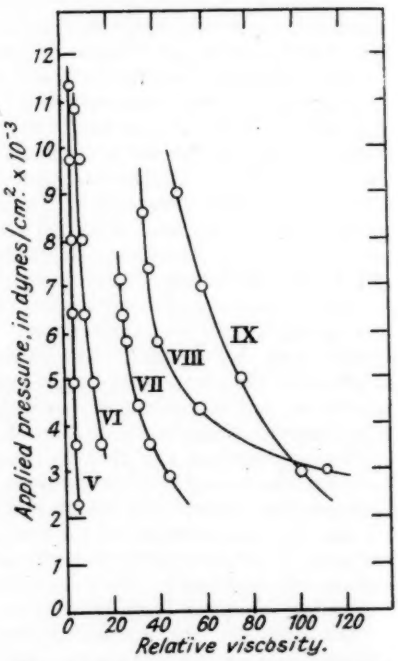
Tetrasodium salt of deoxypentose nucleic acid of calf thymus, ○ *:*

I (*applied pressure* 3000 *dynes/cm.*²), II (*applied pressure* 7000 *dynes/cm.*²).

Tetrasodium salt of deoxypentose nucleic acid after alkaline treatment, III, ● *; after acid treatment,* IV, ◐.

Tetrasodium salt of deoxypentose nucleic acid of calf thymus supplied by Professor Caspersson, IV, ◑.

FIG. 4.



Increase of viscosity of a solution of the tetrasodium salt of deoxypentose nucleic acid on standing at pH 7·0 *after alkaline treatment :* V, *after* 25 *mins. ;* VI, *after* 18 *hours ;* VII, *after* 42 *hours ;* VIII, *after* 91 *hours ;* IX, *original solution of tetrasodium salt of deoxypentose nucleic acid.*

Discussion.—The results of the viscosity measurements are interpreted qualitatively in view of the fact that the viscosity was not a function of the concentration alone over the range of concentration studied, and for such examples the theoretical treatment of viscosity data is very incomplete (Eirich, *Rep. Prog. Physics*, 1940, **7**, 329). Signer, Caspersson, and Hammarsten (*Nature*, 1938, **141**, 122) have applied one of the formulæ relating viscosity with the size and shape of the molecule, but we have not felt entitled to adopt such procedure in view of the much greater structural viscosity of solutions of our material as compared with that of the sample supplied by Professor Caspersson.

The evidence obtained by electrometric titration (Gulland, Jordan, and Taylor, *loc. cit.*) suggests that in the original nucleic acid hydrogen bonds exist between the amino- and hydroxyl groups of nucleotides, and that these bonds are broken at reactions more acid than pH 5 and

more alkaline than pH 11. The addition of acid or alkali did not lower the viscosity of solutions of deoxypentose nucleic acid until these critical pH values were reached.

The reduction in viscosity and in streaming birefringence could be explained by the rupture of hydrogen bonds between adjacent chains, producing units of lower molecular weight and greater symmetry. It is also conceivable that a rolling-up of a single polynucleotide chain could occur, following the fission of hydrogen bonds between nucleotides in that chain, thus reducing the molecular asymmetry but not the molecular weight. The present data do not reveal which of these alternatives is correct or whether both processes occur.

It is most improbable that when a solution of the sodium salt of deoxypentose nucleic acid is restored to pH 7 after acid or alkaline treatment, aggregation will produce precisely the same structure as existed in the original nucleic acid micelle, and it is likely that water molecules will play a greater part in the structure of the new micelle. Subsequent precipitation of the material at pH 7·0 by the addition of ethyl alcohol, followed by drying of the product, may thus considerably alter the structure of the micelle, and it is not surprising therefore that in solution the material isolated by precipitation behaved differently from the non-precipitated product.

The decrease in viscosity on the addition of sodium chloride cannot have been caused by a disaggregation of the type described above, since no titratable groups were produced (Gulland, Jordan, and Taylor, *loc. cit.*). At least three explanations of this decrease are possible, a disaggregation of coarse aggregates of micelles, a change in the shape of the micelle, or a change in the structure of the ion atmosphere and the hydrosphere. The data so far obtained do not permit a choice between these alternatives.

Experimental.

The determination of viscosity was made in a viscometer similar to that described by Frampton (*J. Biol. Chem.*, 1939, **129**, 233). Four viscometers were employed, having capillaries 14·6, 13·4, 14·5, and 12·0 cm. long and the following radii: 0·0390, 0·0476, 0·0575, and 0·0965 cm. respectively. The time for the liquid meniscus to fall between two marks etched on the upright tubes at a known distance apart (*ca.* 0·5 cm.) was measured with a stop watch, reading in 1/10 secs., the meniscus being followed by a travelling microscope. In the experimental results recorded in the figures, the geometric means of the initial and final hydrostatic pressures, between which the viscosity was determined, are recorded.

Streaming birefringence was determined by stirring mechanically a solution placed in a small cell on the stage of a polarising microscope.

The preparation of the materials employed has been described in Parts I and II (this vol., pp. 1129, 1131)

It is a pleasure to record our thanks to the British Empire Cancer Campaign for a maintenance grant to one of us (J. M. C.) and for defraying a part of the expenses of this investigation, and to Imperial Chemical Industries Ltd. for the loan of apparatus.

University College, Nottingham. [*Received, November 2nd*, 1946.]

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215. *The Crystal and Molecular Structure of Certain Dicarboxylic Acids. Part III. Diacetylenedicarboxylic Acid Dihydrate.*

By J. D. Dunitz and J. Monteath Robertson.

The crystal and molecular structure of diacetylenedicarboxylic acid dihydrate, $HO_2C{\cdot}C{\equiv}C{-}C{\equiv}C{\cdot}CO_2H,2H_2O$, has been determined from *X*-ray data, and is shown to be similar in general outline to that of oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate (Parts I and II, this vol., pp. 142, 148). A network of hydrogen bridges extends throughout the crystal and links the water molecules (or oxonium ions) to the adjoining acid molecules.

In the present crystal there is, however, a space-group change, from C_{2h}^5 to C_{2h}^6, and the molecules possess a two-fold axis of symmetry instead of a centre. The configuration is no longer coplanar, the carboxyl groups at opposite ends of the molecule lying nearly in two planes inclined to one another at about 57°.

The bond distances within the molecule are shown in Fig. 3, and should be accurate to within about ± 0·05 A., except in the carbon chain [C(2)–C(1) and C(1)–C(1′)] where a considerably higher accuracy of about ± 0·02 A. should apply. The central single bond of 1·33 A. is the shortest formal single bond so far discovered. This result is discussed, and also the question of whether the carbon–carbon triple bond in acetylene itself is really a suitable standard for the " normal " triple bond type.

In previous papers (*loc. cit.*) we have discussed the structure of oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate and shown that they are of the same type. The two water molecules (or oxonium ions) are situated between the carboxyl groups of adjoining acid molecules, to which they are bound by one very strong and two rather weaker types of hydrogen

bridge. These connections form a spiral network which extends throughout the crystal and confers considerable stability on the whole structure. In these crystals the acid molecules possess a centre of symmetry, the carboxyl groups are nearly symmetrical, and the whole molecule is either planar or very nearly so, as would be expected from general chemical evidence.

We have now completed a similar detailed study of diacetylenedicarboxylic acid dihydrate. In this structure there is a space-group change, from $C_{2h}^5(P2_1/a)$ to $C_{2h}^6(I2/c)$ and a consequent doubling of the c axis. At first sight, and indeed in the principal projection of the structure (Fig. 1), the whole arrangement appears to be entirely analogous to that of the other two structures, apart from the lengthened carbon chain and the c axis doubling. The analysis of the principal zone, ($h0l$), offers no particular difficulty, and proceeds on the same lines as before. In attempting to explain the intensities of other zones of reflections, however, serious difficulties were encountered. These could only be resolved on the assumption that the molecule of diacetylenedicarboxylic acid does not contain a symmetry centre and that the two carboxyl groups are not coplanar but lie in two planes inclined to one another at about 57°. The opposite ends of the molecule are related by a two-fold axis of symmetry which passes through its centre. In Fig. 1 the projection of this two-fold axis gives rise to a centre of symmetry and makes this picture precisely analogous to those already described for the other structures.

This change in configuration is difficult to understand, particularly as the bond-length measurements indicate that resonance effects extend throughout the molecule and these should tend to produce a coplanar form. As discussed more fully below, the configuration adopted in this case appears to be governed by the strongly directed intermolecular hydrogen bridging which exists in the crystal.

Apart from these curious effects, this structure is of special interest in providing fairly reliable measurements on a system of conjugated triple bonds. The linear carbon chain lies in the (010) plane, and two-dimensional Fourier methods provide excellent resolution of the various atoms. Both the triple bonds and their connecting link are found to be somewhat shorter (Fig. 3) than previous measurements on other compounds have indicated. These facts are discussed more fully below after the structure has been described.

Description of the Structure.—Crystal data. Diacetylenedicarboxylic acid dihydrate, $C_6H_2O_4,2H_2O$; M, 174·1; m. p. (decomp. with charring) 95—100°; d, calc. 1·43, found 1·43—1·45; monoclinic prismatic, $a = 11{\cdot}15 \pm 0{\cdot}03$, $b = 3{\cdot}75 \pm 0{\cdot}01$, $c = 20{\cdot}18 \pm 0{\cdot}08$ A., $\beta = 107{\cdot}0° \pm 0{\cdot}5°$. Absent spectra, ($hkl$) when $h + k + l$ is odd; ($h0l$) when either h or l is odd. Space-group, $C_s^4(Ic)$ or $C_{2h}^6(I2/c)$. (C_{2h}^6 assumed in this analysis.) Four molecules per unit cell. Molecular symmetry, centre or two-fold axis. (Two-fold axis assumed in this analysis.) Volume of unit cell, 806·7 A.^{3}. Absorption coefficient for X-rays, $\lambda = 1{\cdot}54$, $\mu = 13{\cdot}4$ cm.$^{-1}$. Total number of electrons per unit cell = F(000) = 360.

Diacetylenedicarboxylic acid was first prepared by Baeyer (*Ber.*, 1885, **18**, 676, 2270) and his method of preparation was followed. Our final product, however, was not identical with that obtained by Baeyer, his being described as the monohydrate while ours was without doubt the *dihydrate*.

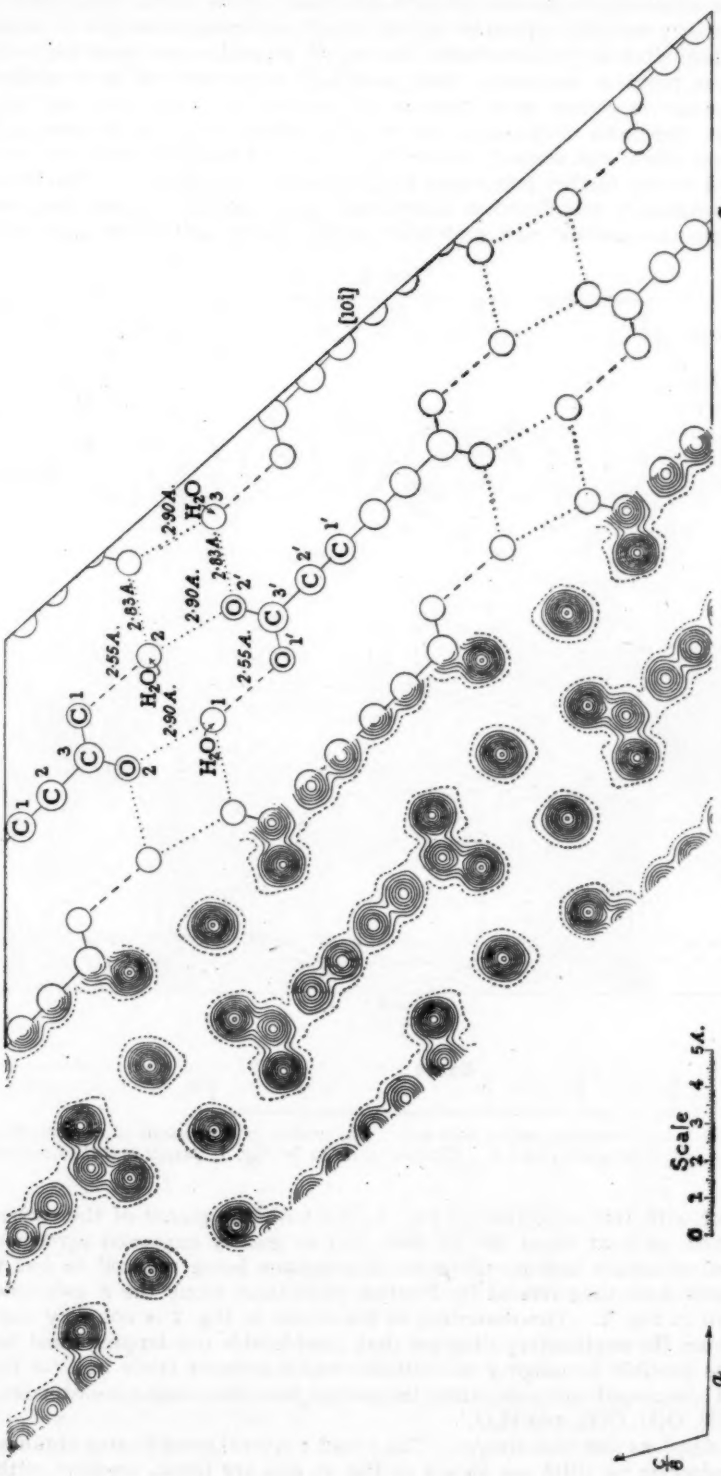
Crystals were obtained from water as small, faintly pink or yellow, sword-like needles, elongated in the b-axis direction. The (001) face was always prominently developed and the (101) also appeared, other faces being generally absent. The crystals deepen in colour when exposed to light, becoming purple and eventually black; exposure to X-rays causes them to become quite black almost immediately.

Structure analysis. The dimensions of the unit cell compared with oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate suggested that the main features of the structure were the same as in these two compounds (see Table I, Part I, *loc. cit.*). The inclination of the [10$\bar{1}$] axis to the a axis is still about 50° and the increase in its half-length (the c axis is doubled) as compared with acetylenedicarboxylic acid dihydrate (2·55 A.) is again just about the amount required to accommodate an extra pair of carbon atoms.

A trial model set up on the assumption that the long axis of the molecule was lying along [10$\bar{1}$] with the planes of the carboxyl groups inclined at about 30° to the (010) plane gave good agreements for the observed ($h0l$) intensities. The x and z co-ordinates were then refined by two successive Fourier syntheses, giving projections on the (010) plane. The final projection is shown in Fig. 1, from which accurate values of these co-ordinates can be obtained.

To determine the y co-ordinates in the structure, it is necessary to decide between certain alternative arrangements that are possible in the space-group C_{2h}^6. The centres of the molecules must lie on special positions, but these may be (*a*) the centres of inversion on the glide plane a, (*b*) the centres of inversion on the glide plane c, (*c*) the two-fold rotation axes. This choice of

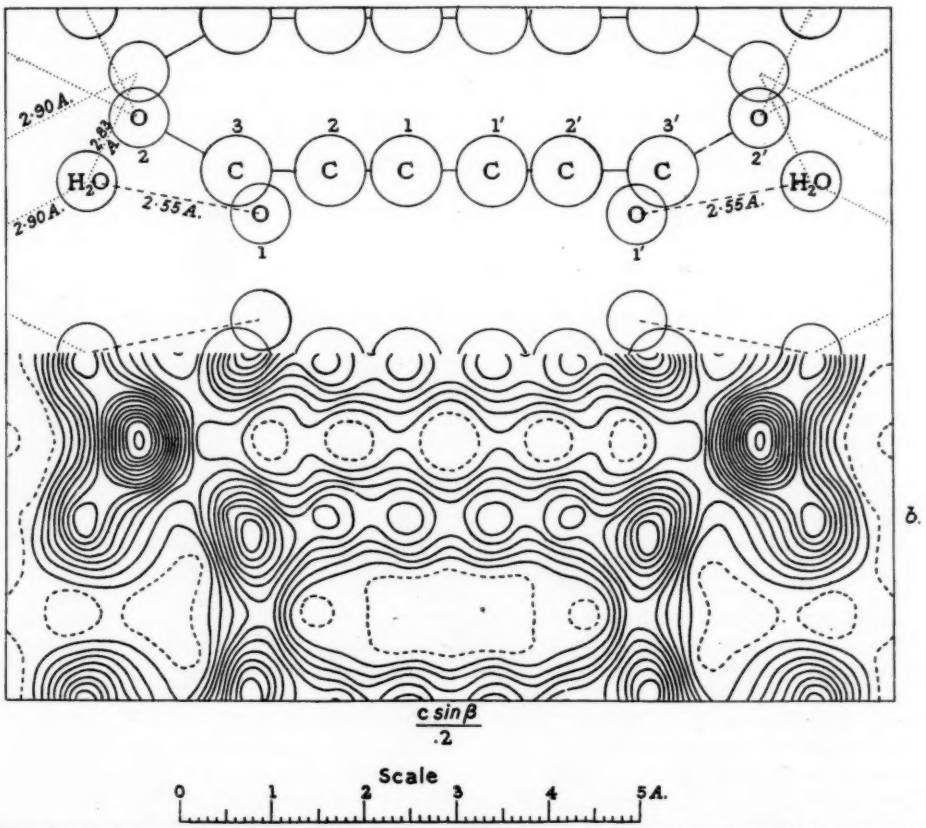
FIG. 1.



Projection along the b *axis, on the* (010) *plane, covering one unit cell. Each contour line represents a density increment of approximately one electron per* Å.^{2}, *the one-electron line being dotted.*

origins does not affect the projection on (010) described above, but it does affect the general planes and especially the (0*kl*) structure factors, which were next examined in detail. Alternative (*a*) was eliminated by trial methods, and as (*b*) seemed much more likely than (*c*), by analogy with the previous structures, this possibility was examined in considerable detail. It was not possible to obtain good agreements between the calculated and the observed structure factors, the mean discrepancy always being about 30%. A Fourier projection was made, using terms whose sign seemed reasonably certain, but this projection was unsatisfactory and did not lead to any further refinement of the assumed co-ordinates. The idea of a molecular centre of symmetry was therefore abandoned, and possibility (*c*) was next explored. A two-fold rotation axis permits new molecular configurations and it was soon found that a

FIG. 2.



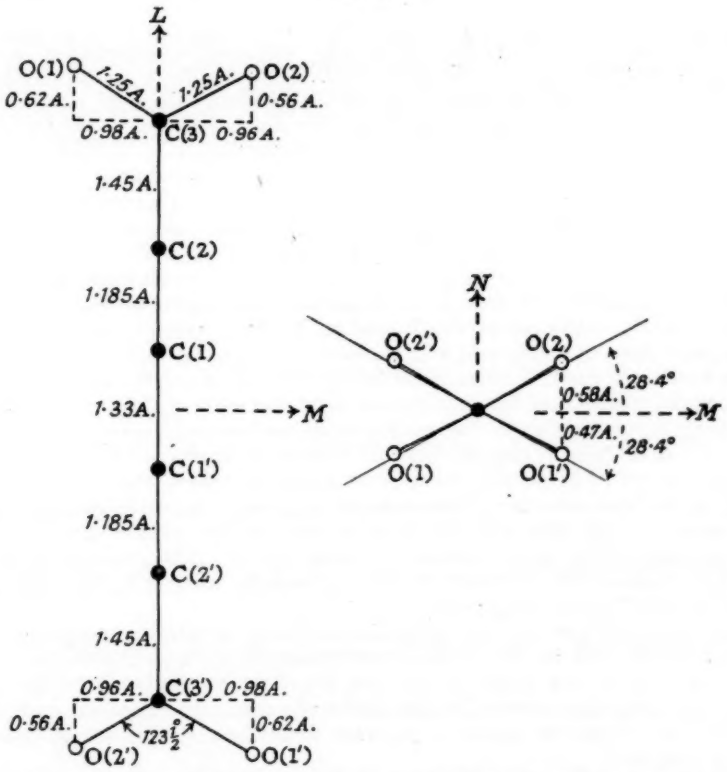
Projection along the a *axis, covering half a unit cell. The centres of the molecules are situated on rotation axes, at* 0·11 A. *from the glide plane* c. *Contour scale as in Fig.* 1, *except that the two-electron line is dotted.*

model, consistent with the projection in Fig. 1, but with the planes of the carboxyl groups oppositely inclined, each at about 30° to (010), led to greatly improved agreements for the (0*kl*) and general structure factors, the mean discrepancy being reduced to less than 20%. The *y* co-ordinates were then refined by Fourier projections along the *a* axis, and the final diagram is shown in Fig. 2. The resolution of the atoms in Fig. 2 is not very complete, and it will be seen from the explanatory diagram that considerable overlapping must be expected. It is nevertheless possible to assign *y* co-ordinates which account fairly well for the shape of the contours. These co-ordinates are rather less certain than the *x* and *z* co-ordinates, especially for the atoms C(3), O(1), O(2), and H_2O.

Molecular dimensions and co-ordinates. The *x* and *z* crystal co-ordinates obtained from the final Fourier projection on (010) are shown in Fig. 5, and are listed, together with the *y* co-ordinates, in Table I. These co-ordinates lead to the molecular model given in Fig. 3 and

to the intermolecular distances of Fig. 1. The orientation of the molecule in the crystal is given in Table II, the molecular axis L being the direction of the carbon chain, N the direction of the two-fold rotation axis, and M the normal to the LN plane. Molecular co-ordinates referred to these axes are given in Table III.

FIG. 3.



Dimensions of the diacetylenedicarboxylic acid molecule Projections of the molecule are drawn on the LM *and* MN *planes.*

TABLE I.

Observed co-ordinates. Centre of symmetry on glide plane c as origin; x, y, z are referred to monoclinic crystal axes a, b, c; x', y, z' are referred to the a and b crystal axes and their perpendicular c'.

Atom (cf. Fig. 1).	x, A.	y, A.	z, A.	x', A.	z', A.	$\frac{2\pi x}{a}$.	$\frac{2\pi y}{b}$.	$\frac{2\pi z}{c}$.
C(1)	0·332	0·11	4·555	−0·999	4·355	10·7°	10·5°	81·3°
C(2)	0·920	0·11	3·687	−0·157	3·525	29·7	10·5	65·8
C(3)	1·642	0·11	2·625	0·875	2·51	53·0	10·5	46·8
O(1)	2·856	−0·36	2·899	2·009	2·772	92·2	−34·6	51·7
O(2)	1·046	0·69	1·503	0·607	1·436	33·8	65·4	26·8
H_2O	3·945	0·00	0·920	3·676	0·880	127·4	0	16·4
Centre of molecule ...	0	0·11	5·045	−1·475	4·824	0	10·5	90·0

TABLE II.

Orientation of the molecule in the crystal. The symbols χ_L, ψ_L, ω_L; χ_M, ψ_M, ω_M; χ_N, ψ_N, ω_N have the same meanings as in Part II, Table II.

$\chi_L = -44{\cdot}5°$ $\cos\chi_L = 0{\cdot}7133$	$\chi_M = -134{\cdot}5°$ $\cos\chi_M = -0{\cdot}7009$	$\chi_N = 90°$ $\cos\chi_N = 0$
$\psi_L = 90°$ $\cos\psi_L = 0$	$\psi_M = 90°$ $\cos\psi_M = 0$	$\psi_N = 0°$ $\cos\psi_N = 1$
$\omega_L = -134{\cdot}5°$ $\cos\omega_L = -0{\cdot}7009$	$\omega_M = 135{\cdot}5°$ $\cos\omega_M = -0{\cdot}7133$	$\omega_N = 90°$ $\cos\omega_N = 0$

TABLE III.

Co-ordinates referred to orthogonal molecular axes L, M, N. The origin of these co-ordinates is situated in the crystal at $x = 0$, $y = 0{\cdot}11$ A., $z = 5{\cdot}045$ A. $(c/4)$.

	L, A.	M, A.	N, A.		L, A.	M, A.	N, A.
C(1)	0·665	0	0	O(1)	3·92	−0·98	−0·47
C(2)	1·85	0	0	O(2)	3·86	0·96	0·58
C(3)	3·30	0	0				

Discussion of Results.—Hydrogen bonding and molecular configuration. Comparison of Fig. 1 with the corresponding projections for oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate (Part I, Fig. 1, and Part II, Fig. 1) shows that the same type of structure appears to exist in all three crystals. So far as the intermolecular hydrogen bonding is concerned, the three crystals are almost identical, the relevant distances in diacetylenedicarboxylic acid dihydrate being O(1)–H_2O = 2·55 A., O(2)–H_2O = 2·90 A. and 2·83 A., almost exactly the same as in acetylenedicarboxylic acid dihydrate. The spiral arrangement described in Parts I and II is exactly reproduced in this compound, the apparently closed circuit O(1), H_2O, O(2′), C(3′), O(1′), H_2O, O(2), C(3), O(1) being actually a spiral which returns to an atom one translation along the b axis from the original atom; the closed four-membered ring formed by the weaker bonds of 2·83, 2·90, 2·83, 2·90 A. is again exactly analogous to the previous cases.

The molecule of diacetylenedicarboxylic acid is, however, clearly different in its geometric configuration from those of oxalic acid and acetylenedicarboxylic acid, which possess a centrosymmetric coplanar structure; even in those structures postulated for oxalic acid with a central bond of the normal single-bond distance the essential planarity of the molecule is not doubted (Part I), although in some of its salts the oxalate group has been reported non-coplanar (Hendricks and Jefferson, *J. Chem. Physics*, 1936, **4**, 102). The diacetylenedicarboxylic acid molecule is found to possess not a centre of inversion, but a two-fold rotation axis, and the carboxyl groups at opposite ends of the molecule do not lie in the same plane. If two planes are taken, passing through the linear carbon chain and oppositely inclined to the (010) or LM plane at an angle of 28·4°, the carboxyl groups lie one on each of these planes. (The observed co-ordinates show that the oxygen atoms of the carboxyl groups are actually at 0·05 A. from these planes, but this deviation is probably not significant.)

The normal configuration for this molecule is almost certainly a coplanar one. A conjugated system of the type shown by diacetylenedicarboxylic acid should confer appreciable double-bond character on the single bonds, and the distances observed in the carbon chain, which are further discussed below, show that this is the case. In the absence of any distorting forces such as steric or similar effects, a coplanar structure therefore seems clearly indicated as being the most stable.

It is seen from Fig. 4(c) that a planar centrosymmetric molecule in the space group C_{2h}^6 would lead to a system of hydrogen bonding in the form of a closed circuit, different from that observed in oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate, where infinite spirals of hydrogen bonds occur. Now the structure shown in Fig. 4(c) is a possible structure, and the fact that it does not occur in the crystal shows that it must have a higher total energy than the structure of Fig. 4(b). The non-coplanar configuration for the molecule is, on the other hand, almost certainly of a higher energy than a coplanar configuration, and the energy difference between these two configurations must be more than compensated by the energy difference between the two possible systems of hydrogen bonding. It seems clear that intermolecular hydrogen bonding must be the governing factor in this type of crystal structure, and that it is sufficiently stable and invariant to cause appreciable distortion from the natural coplanar shape of the molecule.

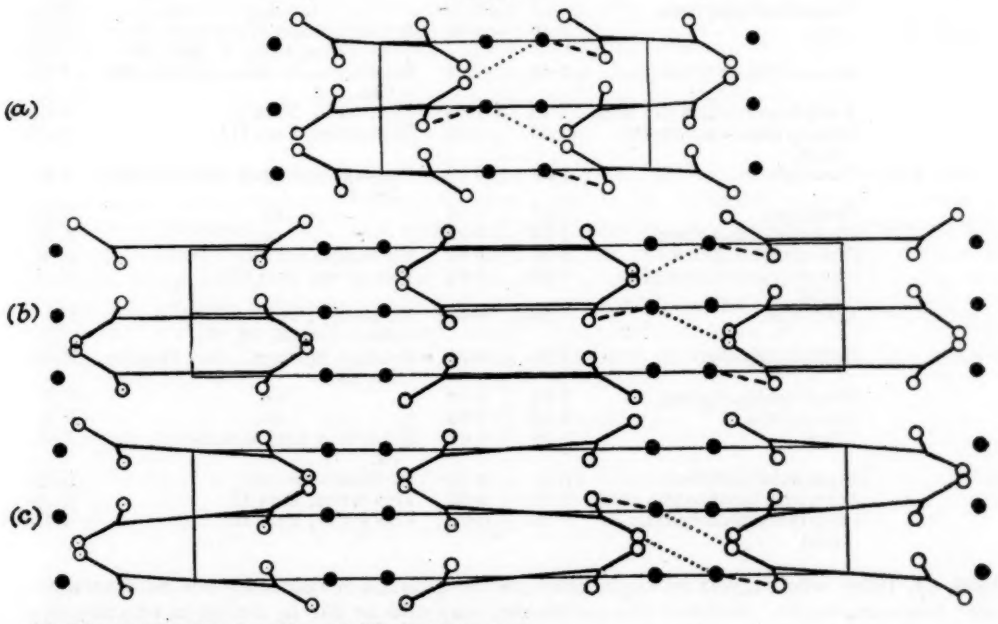
The strong directive power of hydrogen bonds has previously been noted as being able to preserve an open crystal structure which collapses, either partly as in resorcinol (Robertson and Ubbelohde, *Proc. Roy. Soc.*, 1938, *A*, **167**, 122, 136) or completely as in ice, on breaking the bonds by heating. In diacetylenedicarboxylic acid dihydrate the directive power of the hydrogen bonds is sufficient to produce considerable distortion in the molecule itself. Such a directive power seems to indicate a certain amount of covalent character in the hydrogen bond.

The above argument may explain why the expected coplanar configuration for the molecule may not occur in the space-group C_{2h}^6, but it gives no reason for the change in space-group from C_{2h}^5 in which the other compounds in this series occur. We would expect that the centrosymmetric planar molecule with an infinite spiral arrangement of the hydrogen bonds should exist in the space-group C_{2h}^5 with a lower energy than that of the structure observed.

Bond lengths within the molecule. In the carboxyl group we are again unable to distinguish between the carbon–oxygen bond lengths and find them both 1·25 A. (In acetylenedicarboxylic acid dihydrate these bonds were 1·26 and 1·27 A., and in oxalic acid dihydrate, 1·24 and 1·25 A.; see Parts I and II.) The uncertainty here is of the same order as before, *viz.*, about 0·05 A., but the three results taken together seem to indicate that the carbon–oxygen distances in the carboxyl group are probably equal, and support the view that the structures are likely to be ionic.

In the carbon chain the distance C(2)–C(3), measured as 1·45 A., is also rather uncertain, but the fact that it is found to be slightly greater than the corresponding distance in acetylenedicarboxylic acid (1·43 A.) may be significant. In the diacetylenedicarboxylic acid molecule the atoms no longer lie in one plane. The amount of double-bond character in the bond C(3)–C(2) must therefore be reduced with a consequent increase in the length of the bond.

FIG. 4.



(a) *The acetylenedicarboxylic acid dihydrate structure.*
(b) *The diacetylenedicarboxylic acid dihydrate structure.*
(c) *A hypothetical diacetylenedicarboxylic acid dihydrate structure with a coplanar molecule in the space-group* C_{2h}^{6}.

These diagrams show one unit cell of the structures projected along the a *axis. Oxygen atoms are shown as open circles, water molecules as black circles. For the sake of clarity only one hydrogen bond circuit (dotted lines) is shown in each case.*

A considerably higher accuracy, probably to within about 0·02 A., should apply to the remaining bond length measurements. The results are rather unusual, and for comparison Table IV shows the values which have been reported during the last few years for the various types of bond involved in triple-bonded systems.

We should expect bonds of the type ≡C–C< and >C–C≡ to be considerably shortened from the normal single-bond distance of 1·54 A., and the values found in the present investigation and for acetylenedicarboxylic acid are indeed much lower than 1·54 A. The central bond of 1·33 ± 0·02 A. is the shortest formal single bond yet reported, and it is, in fact, of just the length usually associated with a pure double bond. Accepting the value of 1·36 ± 0·03 A. for this bond in diacetylene (Table IV), we might expect some further shortening in the present compound, due to the extra conjugation effects of the carboxyl groups. Wiebenga's value of 1·39 ± 0·03 A. in diphenyldiacetylene seems rather high.

It should be noted that the general problem of contractions in triple-bonded systems has been given an alternative treatment by Conn, Kistiakowsky, and Smith (*J. Amer. Chem. Soc.*,

TABLE IV.

Bond-length measurements in triple-bonded systems.

[*X*-Ray = *X*-Ray crystal analysis. Sp. = Spectroscopic measurements. E.D. = Electron-diffraction measurements (vapours).]

Bond type.	Compound.	Bond distance, A.	Reference.	Method.
≡C—C≤	Methylacetylene	1·462 ± 0·002	Herzberg, Patat, and Verleger, *J. Physical Chem.*, 1937, **41**, 123.	Sp.
		1·462 ± 0·002	Badger and Bauer, *J. Chem. Physics*, 1937, **5**, 594.	Sp.
		1·46 ± 0·02	Pauling, Springall, and Palmer, *J. Amer. Chem. Soc.*, 1939, **61**, 927.	E.D.
	Dimethylacetylene	1·47 ± 0·02	do.	E.D.
	Dimethyldiacetylene	1·47 ± 0·02	do.	E.D.
≡C—C	Tolan	1·40 ± 0·02	Robertson and Woodward, *Proc. Roy. Soc.*, 1938, *A*, **164**, 436.	*X*-Ray
	Diphenyldiacetylene	1·44 ± 0·03	Wiebenga, *Z. Krist.*, 1940, **102**, 193.	*X*-Ray
	Acetylenedicarboxylic acid	1·43 ± 0·04	This series, Part II.	*X*-Ray
	Diacetylenedicarboxylic acid	1·45 ± 0·05	This series, Part III.	*X*-Ray
≡C—C≡	Diacetylene	1·36 ± 0·03	Pauling, Springall, and Palmer, *loc. cit.*	E.D.
	Cyanogen	1·37 ± 0·02	do.	E.D.
	Dimethyldiacetylene	1·38 ± 0·03	do.	E.D.
	Diphenyldiacetylene	1·39 ± 0·03	Wiebenga, *loc. cit.*	*X*-Ray
	Diacetylenedicarboxylic acid	1·33 ± 0·02	This series, Part III.	*X*-Ray
—C≡C—	Acetylene	1·204 ± 0·002	Herzberg, Patat, and Spinks, *Z. Physik*, 1934, **92**, 87.	Sp.
	Methylacetylene	1·20 ± 0·03	Pauling, Springall, and Palmer, *loc. cit.*	E.D.
	Dimethyldiacetylene	1·20 ± 0·02	do.	E.D.
	Diacetylene	1·19 ± 0·03	do.	E.D.
	Tolan	1·19 ± 0·02	Robertson and Woodward, *loc. cit.*	*X*-Ray
	Diphenyldiacetylene	1·18 ± 0·03	Wiebenga, *loc. cit.*	*X*-Ray
	Acetylenedicarboxylic acid	1·19 ± 0·02	This series, Part II.	*X*-Ray
	Diacetylenedicarboxylic acid	1·185 ± 0·02	This series, Part III.	*X*-Ray

1939, **61**, 1868), who suggest an explanation on the grounds of reduced steric hindrance in the acetylene compounds. Some of the contraction may also be due to change in effective single-bond radius (Robertson and Woodward, *Proc. Roy. Soc.*, 1938, *A*, **164**, 436; Penney and Kynch, *ibid.*, p. 409). The results of Crawford and Rice (*J. Chem. Physics*, 1939, **7**, 437) and of Osborne, Garner, and Yost (*ibid.*, 1940, **2**, 131), who show that for dimethylacetylene there is little or no potential barrier to free rotation of the methyl groups, are also significant in this connection and show that double-bond character in the usual sense need not always be present when there is contraction. In view of these results it becomes easier to reconcile the non-coplanar form of the diacetylenedicarboxylic acid molecule with our bond-length measurements.

For the triple bond we obtain a value of 1·185 ± 0·02 A. in our present investigation, and for acetylenedicarboxylic acid the value was 1·19 ± 0·02 A. In general, the values recorded for the triple bond in carbon compounds (Table IV) are usually less than, and never greater than, the value in acetylene itself (1·204 ± 0·002 A.). On the other hand, we might expect that in such conjugated systems the value should be slightly greater than the normal carbon–carbon triple-bond value (see also Penney and Kynch, *loc. cit.*). Although the limits of error are in all cases such that a value of 1·20 A. is admissible, yet the fact that these values are so consistently low may be significant.

One reason for the discrepancy may be that the acetylene value of 1·204 A. is obtained spectroscopically and may not be exactly comparable to the *X*-ray values (see Robertson and Woodward, *Proc. Roy. Soc.*, 1938, *A*, **164**, 436). As far as possible, however, we try to make allowances for displaced electron distributions in the *X*-ray work.

Another more fundamental reason for the discrepancy may be that acetylene is not a suitable standard on which to base a " normal " triple-bond length. Acetylene shows well-marked

acidic properties and the C–H link must bear considerable ionic character. Structures of the type

$$\overset{+}{H}\overset{-}{C}\equiv C-H \qquad H-C\equiv\overset{-}{C}\overset{+}{H} \qquad \overset{+}{H}\overset{-}{C}\equiv\overset{-}{C}\overset{+}{H}$$

must play some part in this molecule and they should have the effect, by resonance energy and by electrostatic attraction, of increasing the C–H bond strength and decreasing the C–H distance. The observed value for this distance in acetylene is 1·057 A., as against 1·093 A. in methane, although the contraction may be partly due to an increase in the *s* character of the hybridised carbon orbitals.

In a similar way, if these structures are important, the ionic forces involved should lead to some increase in the distance between the carbon atoms. The triple-bond distance observed in acetylene may therefore represent a " stretched " rather than a " normal " triple bond.

The amount of this stretching is extremely difficult to calculate because so many different types of energy are involved. A very approximate treatment may be effected by considering only the coulombic repulsion between the two negatively charged atoms in the structure $\overset{+}{H}\overset{-}{C}\equiv\overset{-}{C}\overset{+}{H}$. It must, of course, be remembered that this structure is less important than the other two mentioned above, on account of the adjacent charges.

We consider the problem as a two-atom one and make use of the Morse function

$$V(r) = D(-2e^{-a(r-\beta)} + e^{-2a(r-\beta)})$$

For the triple bond the dissociation energy D is taken as 190 k.-cals. mol.$^{-1}$. There is considerable doubt about the value of this constant owing to the uncertain value of the heat of sublimation of diamond. The value adopted is approximately that given by Skinner (*Trans. Faraday Soc.*, 1945, **41**, 645) assuming $L = 170$; a is the Morse constant, $\sqrt{K/2D}$, where K is the force constant, taken as 15×10^5 dynes cm.$^{-1}$ or 2180 k.-cals. mol.$^{-1}$ A.$^{-2}$; a thus has the value 2·4, and β is the correct " ideal " bond length corresponding to maximum stability.

The curve for the triple bond in acetylene has an additional term due to the coulombic repulsion of the two negatively charged carbon atoms, and it may therefore be represented as

$$V = 190(-2e^{-2\cdot4(r-\beta)} + e^{-4\cdot8(r-\beta)}) + \frac{(\delta e)^2}{r}$$

where δ = fraction of ionic character in the bond. This function has $(\partial v/\partial r)_\beta = 0$ at $r = 1\cdot20$ A.

or
$$\left(\frac{\partial v}{\partial r}\right) = 4\cdot8 \times 190\{e^{-2\cdot4(1\cdot20-\beta)} - e^{-4\cdot8(1\cdot20-\beta)}\} - \frac{(\delta e)^2}{r^2} = 0$$

or
$$912\{e^{-2\cdot4(1\cdot20-\beta)} - e^{-4\cdot8(1\cdot20-\beta)}\} = \frac{(\delta e)^2}{1\cdot20^2}$$

By graphical solution of this equation for various values of δ the results in Table V were obtained. These figures show that the " ideal " triple-bond distance, β, may be somewhat shorter than the acetylene value.

TABLE V.

δ.	$(\delta e)^2/1\cdot20^2$, k.-cal. mol.$^{-1}$.	β, A.	δ.	$(\delta e)^2/1\cdot20^2$, k.-cal. mol.$^{-1}$.	β, A.
0·10	2·3	1·199	0·30	19·7	1·191
0·20	9·2	1·196	0·40	36·8	1·182

We consider, therefore, that acetylene may not be a suitable standard for the triple-bond length. One compound which might be considered to possess the " normal " triple bond is di-*tert.*-butylacetylene, the synthesis of which has recently been announced by Hennion and Banigan (*J. Amer. Chem. Soc.*, 1946, **68**, 1202). A detailed *X*-ray analysis of this compound would be very interesting.

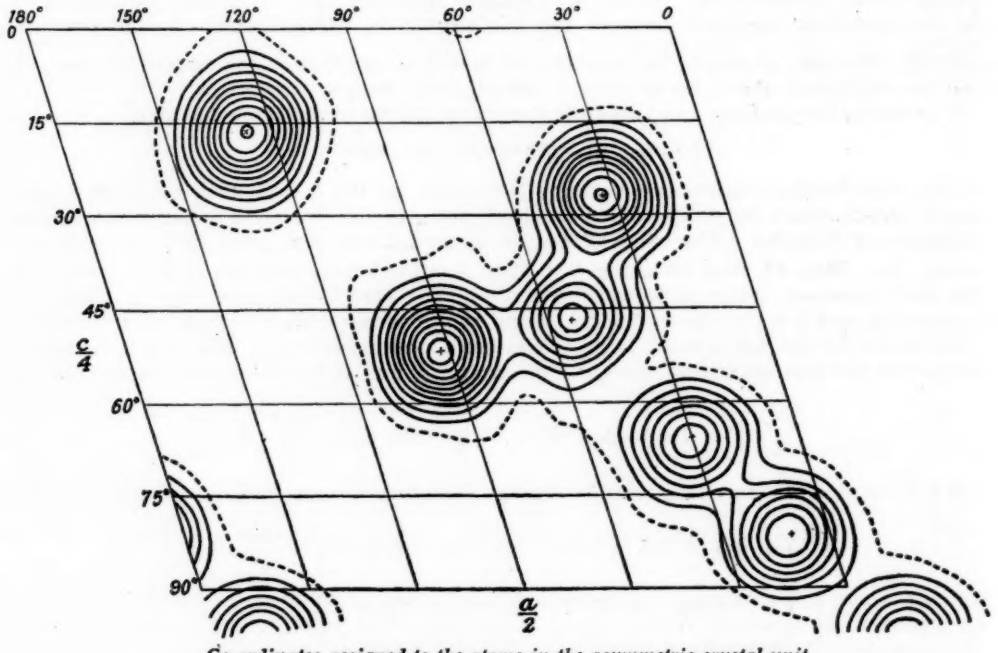
EXPERIMENTAL.

Preparation and Properties.—Diacetylenedicarboxylic acid was prepared by oxidation of the copper compound of propiolic acid with alkaline ferricyanide after Baeyer (*loc. cit.*, p. 2270). The extraction of the acid was difficult and the yields obtained were very poor, being only of the order of a few mg. from about 2 g. of propiolic acid. The compound obtained by us does not correspond to that of Baeyer, which was a monohydrate in the form of rhombic tablets, which darkened at 100°, exploded at 177°, and changed in light to a purple mass. Our product (crystallised from water or aqueous ether–light petroleum) was in the form of pale yellow monoclinic sword-like needles, elongated along the *b* axis. These crystals darkened at 95—100°, decomposed on further heating without explosion, and behaved

similarly to Baeyer's product in light. Microanalysis (Found: C, 41·4; H, 3·8. $C_6H_2O_4,H_2O$ requires C, 46·2; H, 2·6%. $C_6H_2O_4,2H_2O$ requires C, 41·4; H, 3·5%) indicated that our compound is *diacetylenedicarboxylic acid dihydrate*. This was further confirmed by density data; the *X*-ray density for 4 molecules of monohydrate per unit cell is 1·28 g./c.c., or for 4 molecules of dihydrate per unit cell 1·43 g./c.c., while the observed density, determined by flotation in a mixture of ethylene bromide and benzene, is 1·43—1·45 g./c.c.

The crystals became purple on exposure to light and almost black on exposure to *X*-rays. With large crystals exposed to *X*-rays, the blackening was confined to that section of the crystal which was in the actual *X*-ray beam. The nature of the decomposition product was not determined, but its amount must have been very small, since quite black crystals gave *X*-ray photographs which showed no trace of powder rings. Prolonged exposure to *X*-rays did, however, produce photographs complicated by powder rings. The crystals do not lose their water of crystallisation as easily as acetylenedicarboxylic acid dihydrate, but the mosaic character of the crystals is ensured by their decomposition by light and *X*-rays. Copper-$K\alpha$ radiation was used throughout.

FIG. 5.



Co-ordinates assigned to the atoms in the asymmetric crystal unit.

Space-group Determination.—The following photographs were used to determined the unit cell and space-group. Rotation photographs about the *a*, *b*, *c* axes, and about [101], [111], [011] gave the dimensions of the unit cell and showed that this was body-centred. Oscillation photographs about the *b* axis and moving-film photographs of the (0*kl*), (*h*0*l*), and (*h*1*l*) zones showed that the following halvings occurred: (*hkl*) appeared only when $(h + k + l)$ was even; (*h*0*l*) appeared only when both *h* and *l* were even.

These halvings are characteristic of both the space-groups C_{2h}^4 and C_{2h}^5, and these cannot be distinguished by *X*-rays since they differ only in the presence or absence of a centre of symmetry. An experiment to distinguish between these space-groups by pyroelectric effect was inconclusive. Finally, the space-group of higher symmetry C_{2h}^5 was assumed, since the calculations are considerably simplified if the structure possesses a centre of symmetry; we consider this assumption to be justified by the subsequent results.

Intensity Measurements.—Intensity estimates were carried out for the (*h*0*l*) and (0*kl*) zones. For the former the specimen employed had cross-section normal to the *b* axis of 0·13 mm. × 0·31 mm., while that used for the (0*kl*) zone had cross-section normal to the *a* axis of 0·29 mm. × 0·21 mm. The intensities were estimated, and the F values derived from them, in the same way as for acetylenedicarboxylic acid dihydrate (*loc. cit.*). The range of observed intensities was about 3000 to 1.

Fourier Analysis.—The usual formulæ for $\rho(x, z)$ and $\rho(y, z)$ were employed. For $\rho(xz)$ the series was summed at 900 points over the asymmetric unit, an eighth of the unit cell, the axial subdivisions being $a/60 = 0{\cdot}186$ A. and $c/120 = 0{\cdot}168$ A. Three-figure methods (Robertson, *Phil. Mag.*, 1936, **21**, 176) were used, and the positions of the contour lines were plotted on a scale of 5 cm. to 1 A. by graphical interpolation from the arrays of summation totals. The final plot of the asymmetric unit for the *b* projection is shown in Fig. 5, where the final positions assigned to the atoms are indicated by small crosses.

Table VI.

Measured and calculated values of the structure factor.

hkl.	$\sin\theta$ ($\lambda = 1{\cdot}54$).	F, meas.	F, calc.	*hkl.*	$\sin\theta$ ($\lambda = 1{\cdot}54$).	F, meas.	F, calc.
200	0·144	10	− 7	20,14	0·613	10	− 15
400	0·289	52	− 46	20,12	0·536	21	+ 19
600	0·433	34	− 32	20,10	0·460	54	+ 57
800	0·578	27	+ 25	208	0·384	11	+ 9
10,00	0·722	15	− 15	206	0·311	21	− 17
12,00	0·866	11	+ 9	204	0·244	120	+105
020	0·411	60	+ 82	202	0·183	108	−107
040	0·822	8	+ 9	20$\bar{2}$	0·144	39	+ 41
002	0·080	12	+ 5	20$\bar{4}$	0·182	25	+ 33
004	0·160	55	− 58	20$\bar{6}$	0·240	93	− 93
006	0·239	14	− 11	20$\bar{8}$	0·309	98	−102
008	0·319	29	− 29	20,$\bar{10}$	0·380	16	+ 21
00,10	0·399	52	− 60	20,$\bar{12}$	0·456	20	+ 19
00,12	0·479	23	− 20	20,$\bar{14}$	0·534	4	− 3
00,14	0·559	25	+ 25	20,$\bar{16}$	0·613	25	+ 28
00,16	0·638	13	+ 9	20,$\bar{18}$	0·690	44	+ 46
00,18	0·718	10	− 7	20,$\bar{20}$	0·768	18	− 18
00,20	0·798	13	− 7	20,$\bar{22}$	0·847	7	− 8
00,22	0·878	14	+ 11	20,$\bar{24}$	0·925	< 3	− 2
00,24	0·958	< 3	− 2				
				40,20	0·924	7	+ 5
011	0·210	22	− 17	40,18	0·846	4	− 4
013	0·238	32	− 35	40,16	0·772	11	− 9
015	0·287	43	− 51	40,14	0·698	8	+ 9
017	0·347	6	+ 6	40,12	0·624	13	+ 13
019	0·414	34	+ 41	40,10	0·554	11	+ 16
01,11	0·485	12	+ 12	408	0·487	48	+ 47
01,13	0·558	< 8	− 3	406	0·423	23	− 24
01,15	0·633	<10	− 2	404	0·366	18	− 9
01,17	0·709	<10	− 8	402	0·320	119	−118
01,19	0·786	8	− 9	40$\bar{2}$	0·277	16	− 13
01,21	0·863	8	+ 4	40$\bar{4}$	0·288	13	+ 11
01,23	0·941	6	+ 4	40$\bar{6}$	0·317	101	+107
				40$\bar{8}$	0·362	48	+ 52
022	0·419	24	− 21	40,$\bar{10}$	0·419	26	− 30
024	0·442	6	+ 3	40,$\bar{12}$	0·481	< 4	0
026	0·476	24	+ 24	40,$\bar{14}$	0·549	28	+ 27
028	0·521	8	+ 7	40,$\bar{16}$	0·619	41	− 32
02,10	0·573	20	− 21	40,$\bar{18}$	0·689	8	+ 5
02,12	0·631	22	− 29	40,$\bar{20}$	0·765	< 5	+ 2
02,14	0·694	10	− 10	40,$\bar{22}$	0·842	< 4	− 1
02,16	0·759	< 8	+ 1	40,$\bar{24}$	0·916	10	− 9
02,18	0·828	< 8	+ 3				
02,20	0·898	< 8	+ 1	60,18	0·936	8	+ 9
02,22	0·969	8	+ 9	60,16	0·866	5	+ 7
				60,14	0·796	13	− 11
031	0·618	<10	− 1	60,12	0·730	14	− 18
033	0·629	12	+ 10	60,10	0·665	9	− 11
035	0·649	<10	− 7	608	0·606	22	+ 16
037	0·677	<10	0	606	0·549	37	− 42
039	0·714	<10	+ 6	604	0·501	26	+ 27
03,11	0·757	12	− 8	602	0·461	27	+ 20
03,13	0·806	<10	− 4	60$\bar{2}$	0·417	< 5	− 1
03,15	0·860	10	+ 6	60$\bar{4}$	0·422	48	+ 40
03,17	0·917	< 8	+ 1	60$\bar{6}$	0·430	39	+ 34
03,19	0·978	< 6	− 4	60$\bar{8}$	0·458	23	+ 22
				60,$\bar{10}$	0·498	10	+ 7
042	0·827	< 8	+ 1	60,$\bar{12}$	0·544	40	− 42
044	0·838	< 8	+ 5	60,$\bar{14}$	0·599	17	− 17
046	0·857	< 8	− 1	60,$\bar{16}$	0·660	30	− 31
048	0·882	< 8	− 4	60,$\bar{18}$	0·724	9	+ 9
04,10	0·914	< 8	− 1	60,$\bar{20}$	0·791	< 5	+ 3
04,12	0·952	< 6	− 4	60,$\bar{22}$	0·860	5	+ 6
				60,$\bar{24}$	0·930	10	+ 9
20,22	0·925	5	+ 4				
20,20	0·847	8	− 9	80,16	0·972	< 3	− 2
20,18	0·769	15	− 14	80,14	0·908	< 4	+ 1
20,16	0·691	15	− 17	80,12	0·845	< 5	0
				80,10	0·786	30	− 32

TABLE VI.—*continued.*

Measured and calculated values of the structure factor.

hkl.	sin θ (λ = 1·54).	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54).	F, meas.	F, calc.
808	0·734	13	+ 12	10,0,$\bar{4}$	0·691	< 5	+ 5
806	0·684	29	+ 24	10,0,$\bar{6}$	0·689	13	− 13
804	0·640	10	+ 13	10,0,$\bar{8}$	0·696	29	− 29
802	0·605	12	+ 14	10,0,$\bar{10}$	0·715	39	+ 37
80$\bar{2}$	0·559	12	− 5	10,0,$\bar{12}$	0·741	23	+ 18
80$\bar{4}$	0·551	56	− 50	10,0,$\bar{14}$	0·775	5	+ 5
80$\bar{6}$	0·556	28	− 28	10,0,$\bar{16}$	0·815	< 5	+ 1
80$\bar{8}$	0·574	10	+ 8	10,0,$\bar{18}$	0·857	< 5	− 1
80,$\bar{10}$	0·599	22	+ 17	10,0,$\bar{20}$	0·909	3	− 4
80,$\bar{12}$	0·634	28	− 26	10,0,$\bar{22}$	0·961	8	− 8
80,$\bar{14}$	0·678	23	+ 23				
80,$\bar{16}$	0·727	< 5	0	12,06	0·961	< 3	− 3
80,$\bar{18}$	0·781	4	− 5	12,04	0·923	7	− 8
80,$\bar{20}$	0·839	7	+ 7	12,02	0·891	< 4	− 4
80,$\bar{22}$	0·902	< 4	+ 2	12,0$\bar{2}$	0·845	8	+ 7
80,$\bar{24}$	0·966	< 3	+ 2	12,0$\bar{4}$	0·834	< 5	− 1
				12,0$\bar{6}$	0·828	21	+ 15
10,0,12	0·969	< 3	+ 8	12,0$\bar{8}$	0·831	3	− 4
10,0,10	0·914	< 4	+ 3	12,0,$\bar{10}$	0·841	6	− 5
10,08	0·865	5	− 3	12,0,$\bar{12}$	0·860	5	− 4
10,06	0·819	5	− 7	12,0,$\bar{14}$	0·885	6	+ 5
10,04	0·779	6	+ 6	12,0,$\bar{16}$	0·916	3	+ 1
10,02	0·746	6	+ 8	12,0,$\bar{18}$	0·953	9	− 8
10,0$\bar{2}$	0·700	10	− 9				

The y co-ordinates together with a check on the z co-ordinates were obtained from the projection along the a axis shown in Fig. 2. $\rho(yz)$ was summed at 225 points over the asymmetric unit, the axial subdivisions being $b/30 = 0{\cdot}125$ A. and $(c \sin \beta)/60 = 0{\cdot}322$ A. The summations were carried out, and the contour map drawn, as described above for the b projection. Considerable overlapping occurs in the a axis projection and the y co-ordinates are not fixed as rigorously as we should like, but no better resolution can be obtained by two-dimensional methods and any ambiguity can be resolved only by means of three-dimensional Fourier synthesis.

From the final co-ordinates (Table I), all the structure factors were recalculated and the results are given in Table VI. For this calculation the structure factor F has been expressed in the form $fS = F$. For f we have used a composite empirical atomic scattering factor which gives better results than that used in the case of acetylenedicarboxylic acid dihydrate and oxalic acid dihydrate (*q.v.*). The f values used are as follows :

sin θ (λ = 1·54)	0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9	1·0
f	334	282	224	167	113	80	54	34	19	13

The maximum value of f, at $\sin \theta = 0$, may be taken as F (000) = 360, the total number of electrons in the unit cell.

S is the geometric structure factor. It is conveniently put into the form

$$60\,S = \Sigma 8A \cos 2\pi\left(\frac{hx}{a} + \frac{lz}{c}\right) \cos 2\pi\frac{ky}{b}, \text{ when } l \text{ is even}$$

$$60\,S = \Sigma - 8A \sin 2\pi\left(\frac{hx}{a} + \frac{lz}{c}\right) \sin 2\pi\frac{ky}{b}, \text{ when } l \text{ is odd}$$

The carbon and oxygen coefficients are weighted in the ratio of 6 to 9, so that for a carbon atom $A = 1$ and for an oxygen atom $A = 1{\cdot}5$. Since there are six atoms in the asymmetric unit, three of which have $A = 1$ and three $A = 1{\cdot}5$, the maximum value of S is conveniently taken as unity.

The percentage discrepancy finally obtained, expressed as

$$\frac{\Sigma(|\text{F meas.}| - |\text{F calc.}|)}{\Sigma|\text{F meas.}|} \times 100$$

is 11·0 for the ($h0l$) reflections, 14·8 for the ($0kl$) reflections, and 11·9 for all reflections.

In the b axis projection (Fig. 1) the F values for the (80$\bar{2}$) and (10, 0, 8) planes were omitted from the Fourier summation owing to uncertainty of sign.

We thank Dr. E. Warhurst for much helpful discussion during the progress of this work, and one of us (J. D. D.) is indebted to the Carnegie Trustrees for a Scholarship.

UNIVERSITY OF GLASGOW. [*Received, November 14th*, 1946.]

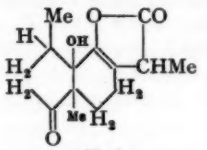
216. *The Constitution of ψ-Santonin. Part IV. A Study of the Butenolide System.*

By Wesley Cocker and Stanley Hornsby.

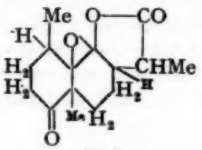
The speeds of bromination and hydrogenation, and the products of the latter, of ψ-santonin and a number of αβ- and βγ-butenolides have been compared. Spectroscopic observations have also been made. Possible structures for ψ-santonin are discussed.

Experiments with dihydro-ψ-santonin suggest that this compound can be represented as (III).

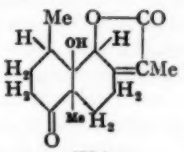
In Part I of this series Clemo and Cocker (*J.*, 1946, 30) discussed the chemistry of ψ-santonin and suggested that one of the structures (I*a*) and (II) represented the constitution of this compound, but it was not then possible to decide which was the more likely.



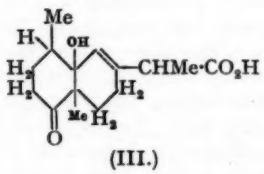
(I*a*.)



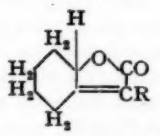
(I*b*.)



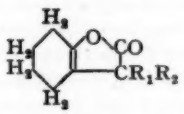
(II.)



(III.)



(IV; R = H; V; R = Me.)



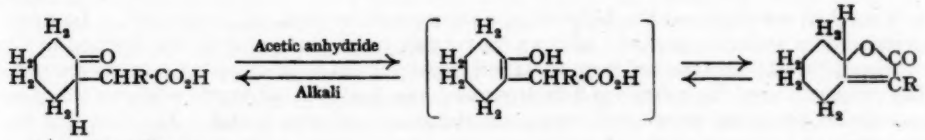
(VI.)

Colour reactions with sodium nitroprusside (cf. Jacobs and Hoffmann, *J. Biol. Chem.*, 1925, **67**, 333; Paist, Blout, Uhle, and Elderfield, *J. Org. Chem.*, 1941, **6**, 273) strongly suggested the presence of a βγ-butenolide, whilst the slow reduction of ammoniacal nitrate suggested an αβ-butenolide (cf. Jacobs, Hoffmann, and Gustus, *J. Biol. Chem.*, 1926, **70**, 1).

In view of these opposing reactions it was felt desirable to study the properties of a number of butenolides of both the αβ- and the βγ-type in which, as in ψ-santonin, the butenolide is fused in the βγ-position to a *cyclo*hexane ring.

Although various α- and β-substituted butenolides have been studied in which the substituent was *cyclo*hexyl (Elderfield *et al.*, *J. Org. Chem.*, 1941, **6**, 289) and a few of the above mentioned fused lactones have been prepared, no systematic study of the properties of the latter compounds seems to have been undertaken. We have therefore prepared and studied the properties of the lactones of the following acids, namely, 2-hydroxy*cyclo*hexylideneacetic acid (IV), 2-hydroxy-*cyclo*hexylidene-α-propionic acid (V), and 2-*hydroxy*cyclo*hex*-1-*enyl*-α-iso*butyric acid* (VI; $R_1 = R_2 = Me$).

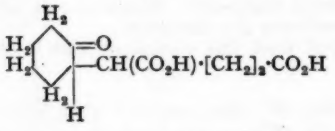
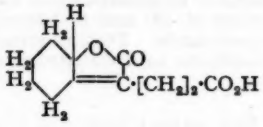
The αβ-butenolides (IV and V) were prepared by the cyclisation of 2-keto*cyclo*hexylmalonic or 2-keto*cyclo*hexyl-α-propionic acid with acetic anhydride; the reactions are apparently as follows:



(R = H or Me.)

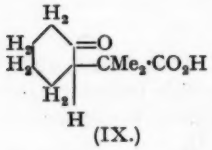
That the product of the cyclisation is an αβ-butenolide is shown by the fact that when the lactone obtained from 2-keto*cyclo*hexylmalonic acid was submitted to ozonolysis in chloroform, 2-keto*cyclo*hexanol was obtained. Although neither glyoxylic nor oxalic acid was obtained in this reaction, yet when the same lactone was oxidised with neutral permanganate a mixture was obtained from which, in addition to some unchanged lactone, an unidentified carbonyl compound, adipic acid, and oxalic acid were isolated. We do not consider that the isolation of adipic acid and oxalic acid is necessarily of diagnostic value, but together with the evidence from the

ozonolysis experiments there is adequate proof of the αβ-butenolide structure. The lactone from 2-keto*cyclo*hexyl-α-propionic acid also gave 2-keto*cyclo*hexanol on ozonolysis. Furthermore, Kendal and Osterberg (*J. Amer. Chem. Soc.*, 1927, **49**, 2047) showed conclusively by ozonolysis experiments on the product that when 2-keto*cyclo*hexyl-α-glutaric acid (VII) is cyclised it yields the αβ-butenolide (VIII), a result which is analogous to those we obtained.

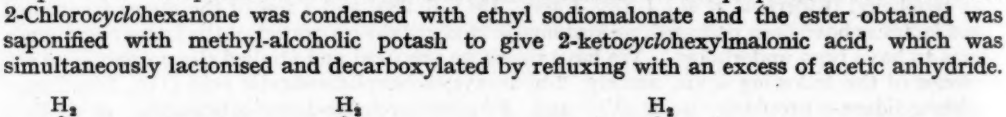
(VII.)  (VIII.) 

Other workers, *e.g.*, Grewe (*Ber.*, 1939, **72**, 426), have concluded that when γ-keto-acids of the type already mentioned are cyclised the result is a βγ-lactone. This worker assumed that the product of cyclisation of 2-keto*cyclo*hexyl-α-benzylacetic acid was (VI; $R_1 = H$; $R_2 = CH_2Ph$). He found, however, that on catalytic hydrogenation the butenolide system was unaffected, whereas the aromatic nucleus suffered reduction. This resistance to hydrogenation was similar to that shown by lactone (V), and we believe that Grewe's lactone was actually of the αβ-butenolide type.

The production of an αβ-butenolide in the manner stated does not appear to be in accordance with the work of Kon and Speight (*J.*, 1926, 2727) who showed that, presumably as a result of the tendency of the six membered ring to acquire a double bond, the equilibrium between *cyclo*hex-1-enylacetic acid and its esters and *cyclo*hexylideneacetic acid and its esters lies on the side of the former compounds. By analogy we should have expected the equilibrium between the βγ- and αβ-butenolides under discussion to lie on the side of the former, but it appears that in these lactones the tendency of the double bond to conjugate with the carbonyl group predominates. It was obvious, therefore, that a βγ-butenolide of type (VI) could only be prepared if the tautomeric system were blocked, *i.e.*, if R_1 and R_2 were groups other than H. We therefore prepared and cyclised 2-keto*cyclo*hexyl-α-*iso*butyric acid (IX) which yielded the required *lactone* (VI; $R_1 = R_2 = Me$).


(IX.)

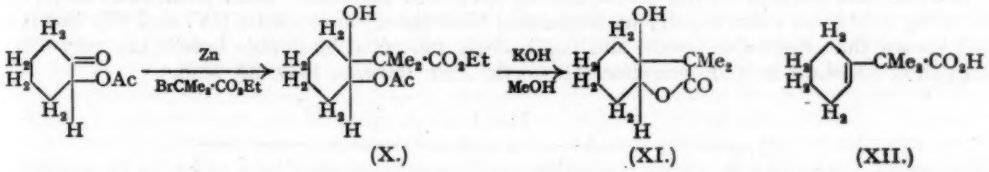
The lactone of 2-hydroxy*cyclo*hexylideneacetic acid (IV) was prepared by McCrae, Charlesworth, and Alexander (*Canadian J. Res.*, 1943, **21***B*, 1) who oxidised the lactone of 2-hydroxy*cyclo*hexylacetic acid (Coffey, *Rec. Trav. chim.*, 1923, **42**, 382) with bromine and magnesium hydroxide. The keto-acid so obtained was then cyclised by heating at 200° in a vacuum, and the butenolide was obtained as a solid, m. p. 7—8°. We preferred to use a more economical method for the preparation of this lactone. 2-Chloro*cyclo*hexanone was condensed with ethyl sodiomalonate and the ester obtained was saponified with methyl-alcoholic potash to give 2-keto*cyclo*hexylmalonic acid, which was simultaneously lactonised and decarboxylated by refluxing with an excess of acetic anhydride.


(IV)

By this method we obtained the butenolide as a crystalline solid, m. p. 29—30°. Lactone (V) was prepared in a similar manner, and we found this to be preferable to the method of Clemo and Cocker (*loc. cit.*) who started from 2-carbethoxy*cyclo*hexanone and ethyl α-bromopropionate.

The preparation of the lactone of 2-hydroxy*cyclo*hex-1-enyl-α-*iso*butyric acid was troublesome and a number of routes were tried before a satisfactory one was found. The first was by the condensation of 2-carbethoxy*cyclo*hexanone in presence of sodium with ethyl α-bromo*iso*butyrate, and the product, which gave only poor analysis results, was hydrolysed with 8% methyl-alcoholic potash. Unfortunately this gave only pimelic acid and a hygroscopic acid which gave no carbonyl reactions. In the second method 2-acetoxy*cyclo*hexanone was condensed in presence of zinc with ethyl α-bromo*iso*butyrate to give *ethyl 1-hydroxy-2-acetoxy*cyclo*hexyl-α-iso*butyrate* (X) in fair yield. All attempts to dehydrate this ester failed. It was boiled with acetic anhydride, with and without anhydrous sodium acetate; it was heated at 160° with potassium hydrogen sulphate; and finally it was heated under reflux with pyridine and phosphoryl chloride: all these treatments left it unchanged. Torrey, Kuck, and Elderfield

(*J. Org. Chem.*, 1941, **6**, 289) found similar difficulty in the dehydration of certain tertiary alcohols, but all their compounds yielded to the dehydrating action of a boiling mixture of pyridine and phosphoryl chloride.



(X.) (XI.) (XII.)

When the ester (X) was hydrolysed with alcoholic potash and the mixture acidified, a lactone $C_{10}H_{16}O_3$ was obtained which presumably was (XI). Attempts to dehydrate this lactone were again unsuccessful, but it was found that on heating it with 30% alcoholic sulphuric acid a very small yield of a carbonyl compound was obtained, and this gave a 2 : 4-*dinitrophenylhydrazone* which proved to be identical with that obtained from 2-keto*cyclo*hexyl-α-*iso*butyric acid. The ketone was probably produced from (XI) by a pinacol–pinacolone rearrangement. The method was, however, of little preparative value.

Finally the required lactone (VI; $R_1 = R_2 = Me$) was obtained by a method similar to that used by McCrae, Charlesworth, and Alexander (*loc. cit.*) for the preparation of (IV). Ethyl 1-hydroxy*cyclo*hexyl-α-*iso*butyrate (Wallach and Mallinson, *Annalen*, 1908, **360**, 68) was obtained by the condensation of *cyclo*hexanone with ethyl α-bromo*iso*butyrate in presence of zinc, and it was dehydrated and then saponified to yield *cyclo*hex-1-enyl-α-*iso*butyric acid. Von Braun and Münch (*Annalen*, 1928, **465**, 55) effected the lactonisation of this acid with hydrogen bromide in acetic acid. We performed the lactonisation with 50% sulphuric acid, and the product was oxidised to 2-keto*cyclo*hexyl-α-*iso*butyric acid. The lactonisation of *cyclo*hex-1-enyl-α-*iso*butyric acid mentioned above was, however, accompanied by the production of 1-*iso*propyl*cyclo*hexene. Wallach and Mallinson (*loc. cit.*) showed that this compound could be obtained from *iso*propylidene*cyclo*hexane by heating with sulphuric acid. Lactone (VI; $R_1 = R_2 = Me$) was finally obtained by the cyclisation of 2-keto*cyclo*hexyl-α-*iso*butyric acid with acetic anhydride.

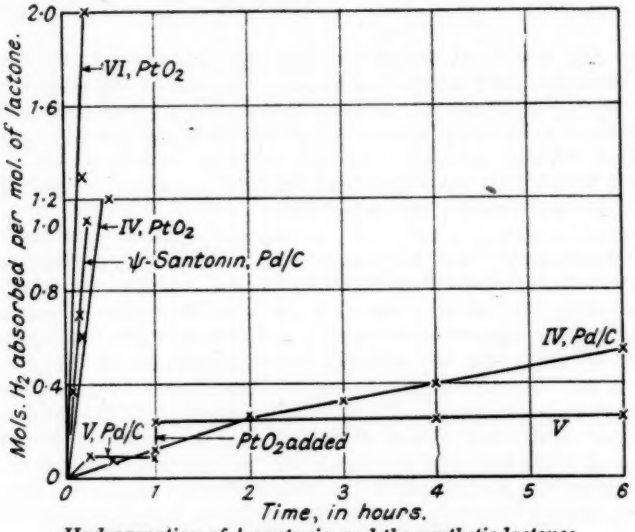
Various attempts were made to prepare the lactone of 1-hydroxy-3 : 4-dihydronaphthalene-2-*iso*butyric acid, but these were unsuccessful.

Hydrogenation Experiments.—ψ-Santonin and the lactones (IV), (V), and (VI; $R_1 = R_2 = Me$) were separately submitted to catalytic hydrogenation at 1 atmosphere pressure of hydrogen, at room temperature using (*a*) palladised charcoal and (*b*) Adams's platinic oxide catalyst. The results of these experiments are shown in Fig. 1 and Table I. It can readily be seen that, of all the lactones employed, only ψ-santonin was hydrogenated with any rapidity when palladised charcoal was employed, and here absorption ceased when one molecule of hydrogen had been taken up. The product of the reaction was dihydro-ψ-santonin (III), an unsaturated carboxylic acid. With the same catalyst the αβ-butenolide (IV) absorbed one molecule of hydrogen in about 16 hours and the product was the saturated lactone of 2-hydroxy*cyclo*hexylacetic acid. On the other hand the αβ-butenolide (V), in which the αβ-double bond is further protected, absorbed about 0·1 molecule of hydrogen in fifteen minutes in presence of palladised charcoal after which no further absorption took place. The addition of Adams's catalyst at this stage effected no further absorption apart from that expected in the reduction of the catalyst. On working up the reaction mixture only (V) was isolated. The βγ-butenolide (VI; $R_1 = R_2 = Me$) was unaffected by hydrogen and palladised charcoal, but in presence of Adams's catalyst absorption took place at a very rapid rate and 2 molecules of hydrogen were taken up in 15 minutes with the production of *cyclo*hexyl-α-*iso*butyric acid, identical with the acid obtained from the hydrogenation of *cyclo*hex-1-enyl-α-*iso*butyric acid (XII) in presence of Adams's catalyst. In presence of the same catalyst ψ-santonin absorbed one molecule of hydrogen at a speed very similar to that of (VI), but further hydrogenation was slower and was complicated by the reduction of the keto-group. Under similar conditions (IV) was reduced rapidly, but not so rapidly as either ψ-santonin or (VI), and again a saturated lactone was obtained. Finally we found that *cyclo*hex-1-enyl-α-*iso*butyric acid (XII) was unaffected by hydrogen and palladised charcoal, which falls into line with the absence of reactivity of dihydro-ψ-santonin (III) towards the same reagents, and it is of interest to record that Thakur (*J.*, 1933, 1481) found that *cyclo*hex-1-enyl-α-propionic acid was only slowly reduced with Adams's catalyst.

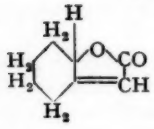
These results clearly indicate that ψ-santonin and the βγ-lactone behave alike in the

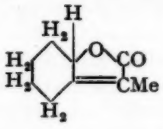
production of a deoxy-acid on hydrogenation; a result which is similar to that found by Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601) in the investigation of a number of simple βγ-butenolides. These workers and Paist, Blout, Uhle, and Elderfield (*loc. cit.*) also found that simple αβ-butenolides are reduced to the corresponding saturated lactones. Both ψ-santonin and (VI; $R_1 = R_2 = Me$) are more rapidly hydrogenated than the αβ-butenolides (IV) and (V), but it is well known that αβ-double bonds, and particularly protected αβ-double bonds, are very often sluggish or resistant to hydrogenation (Haworth, *Ann. Reports*, 1937, **34**, 328).

FIG. 1.



Hydrogenation of ψ-santonin and the synthetic lactones.

IV = 

V = 

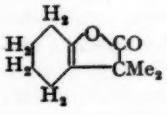
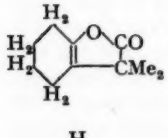
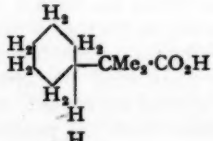
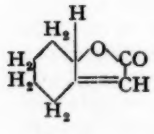
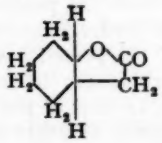
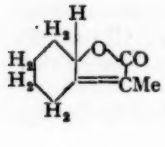
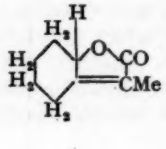
VI = 

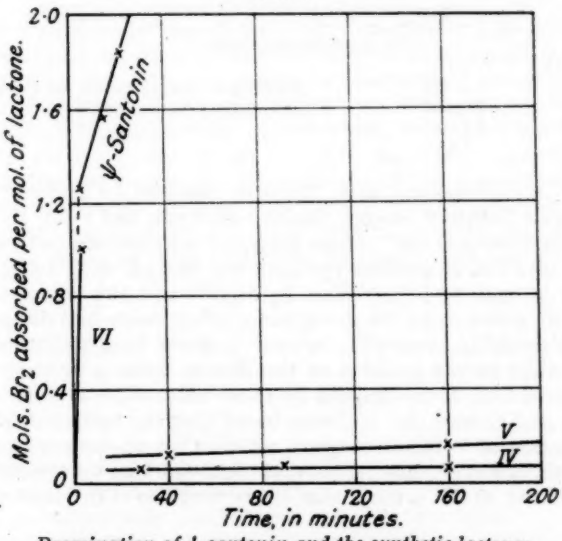
TABLE I.

Hydrogenation Experiments on the Lactones at 1 atm./18°±3°.

Lactone.	Catalyst.	Time for uptake of hydrogen. 1 mol.	2 mols.	Product.
ψ-Santonin	Pd/C	15 minutes		Dihydro ψ-santonin (III)
	PtO_2, H_2O	10 ,,		
	Pd/C	No absorption		
	PtO_2, H_2O		15 minutes	
	Pd/C	16 hours		
	PtO_2, H_2O	30 minutes		
	Pd/C	0·1 mol. in 15 mins.		
	PtO_2, H_2O	No further absorption		

Halogenation Experiments. (With C. LIPMAN.)—It is well known that αβ-unsaturated acids and esters absorb bromine less rapidly than their βγ-isomerides (Sudborough and Thomas, *J.*, 1910, **97**, 715, 2450) and this method was used by Linstead (*J.*, 1927, 355) for determination of the position of equilibrium in mixtures of isomeric unsaturated acids. By a method similar to that advocated by Linstead we have studied the comparative speeds of bromination of ψ-santonin and the three other lactones. For this purpose equivalent quantities (1/1200 g.-mol.) of the lactones in N/60-solution in carbon tetrachloride, containing 30% acetic acid necessary to obtain solution, were treated with 2 mols. of N/15-solution of bromine in carbon tetrachloride, the final concentration of the bromine in the mixture being N/30, and the carefully stoppered vessels were placed in a dark container at 16—17°. Aliquot portions of the solutions were withdrawn at intervals and after treatment with potassium iodide the liberated iodine was titrated with N/40-thiosulphate. 2 Mols. of bromine were employed because ψ-santonin brominates first to give a monobromo-compound by substitution and then one molecule of bromine adds to give a tribromo-compound (Clemo and Cocker, *loc. cit.*). Fig. 2 and Table II

FIG. 2.



Bromination of ψ-santonin and the synthetic lactones.
(IV, V, *and* VI *as for Fig.* 1.)

TABLE II.

Bromine absorption in mols. in x minutes.

Lactone	$x = 5$	10	15	20	30	40	90	160	320	420	900
ψ-Santonin	1·242	—	1·54	1·82	1·99	—	—	—	—	—	—
(VI)	1·11	1·06	—	—	—	—	—	—	—	—	—
(IV)	—	—	—	—	0·04	—	0·06	0·05	—	—	0·15
(V)	—	—	0·11	—	—	0·14	—	0·17	0·19	0·21	—

(IV, V, and VI as for Fig. 1.)

show that ψ-santonin and the βγ-butenolide (VI; $R_1 = R_2 = Me$) absorb bromine at approximately the same rate, although it should be remembered that it is the upper part of the graph of ψ-santonin which must be compared with that of (VI), since the lower part of the ψ-santonin graph, which lies upon that of (VI), represents the substitution reaction. When monobromo-ψ-santonin was brominated using one molecule of bromine its rate of bromination was similar to that found for the absorption of the second molecule of bromine in ψ-santonin itself, so that the influence of the hydrogen bromide produced in the substitution reaction in ψ-santonin need not be considered. When (VI) was brominated with 1 mol. of bromine there was no change in the rate of reaction. The absorption of bromine by the αβ-butenolides (IV and V) is very slow, but the initial rapid absorption is interesting and is paralleled by a similar absorption in the hydrogenation of (V). This is probably due to the presence of some βγ-butenolide in (IV) and (V).

Cavallito and Haskell (*J. Amer. Chem. Soc.*, 1946, **68**, 2332) used Hanus solution (IBr) as a reagent for differentiating between αβ- and βγ-lactones. They found that the latter reacted much more rapidly than the former with this reagent.

The bromination and hydrogenation results seem to be evidence in favour of the adoption of structure (I*a*) for ψ-santonin.

Spectroscopic Evidence.—Spectroscopic studies do not appear to support the βγ-structure, and in fact, neglecting the absorption due to the carbonyl group, there is a striking resemblance between the absorptions of ψ-santonin and the αβ-lactone (V). In each case there is high intensity absorption at the extreme end of the usual ultra-violet range, and in neither is a maximum discernible. This is similar to the experience noted by other workers such as Haynes and Jones (*J.*, 1946, 954) and Ruzicka *et al.* (*Helv. Chim. Acta*, 1942, **25**, 435; 1944, **27**, 186) with a number of simple αβ-unsaturated lactones. The βγ-lactone (VI) absorbs with a much smaller intensity than either ψ-santonin or lactone (V) at comparable wave-lengths.

TABLE III.

Light-absorption Data for Unsaturated Lactones.

(In alcoholic solutions.)

	λ, A.	ε.
ψ-Santonin ...	2900 *	35
	2000 †	14,000
(V)	2200 †	12,000
(VI)	2200 †	3,851

* Maximum characteristic of the isolated >C=O group.
† Maximum not discernible.

Colour Reactions and Reactions with Tollens's Reagent.—Lactones (IV) and (V) both instantaneously reduced Tollens's reagent whilst ψ-santonin and (VI; $R_1 = R_2 = Me$) gave a silver mirror only after twelve hours. These reactions were carried out as follows. A solution of 10 mg. of lactone in 1 c.c. of purified pyridine was treated with 1 c.c. of Tollens's reagent, prepared from equal volumes of 10% sodium hydroxide and 10% silver nitrate to which 10% ammonia was added dropwise until the precipitated silver oxide had disappeared.

The results are interesting since they appear to show that ψ-santonin and lactone (VI; $R_1 = R_2 = Me$) are alike in the position of the double bond (*i.e.*, they are βγ-butenolides), but the slowness of reduction of the reagent by these butenolides is contrary to the experience of Jacobs, Hoffmann, and Gustus (*loc. cit.*) who found that the βγ-butenolides they investigated gave immediate reduction of Tollens's reagent, whereas the αβ-butenolides were very sluggish. It must be remembered, however, that Jacobs and his co-workers were not investigating lactones fused to a *cyclo*hexane ring, and it is more than likely that this is the explanation of the differing results.

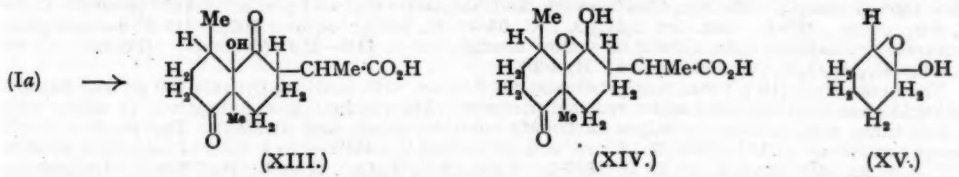
The Legal tests when applied to all the synthetic lactones in the manner recommended by Paist, Blout, Uhle, and Elderfield (*loc. cit.*) were most unsatisfactory. There was little change in colouration with sodium nitroprusside until the solution became distinctly alkaline to phenolphthalein and it is felt that as applied to these particular lactones the Legal test has little diagnostic value.

Cardiac Activity of the Lactones.—The effect on the isolated frog heart of ψ-santonin, the lactones (IV), (V), (VI), and the lactone of 2-hydroxy*cyclo*hexylacetic acid was tried through the courtesy of the late Dr. J. Secker of the Department of Physiology of King's College. The concentration of lactone used was 1 mg. per c.c. of 10% aqueous alcohol and it was found that 1 drop of solution of all the butenolides produced cardiac inhibition, whilst the saturated lactone was ineffective. It appears, therefore, that the unsaturated lactone system has some cardiac effect, but it is not specific for either the αβ- or the βγ-type. No experiments were performed on cats but it is highly unlikely that any of the lactones would have important effects (cf. Swain, Todd, and Waring, *J.*, 1944, 548).

If the βγ-butenolide structure (I) for ψ-santonin is adopted there are certain experimental results which require an explanation. In the first place when ψ-santonin is saponified with methyl-alcoholic potash a solution is obtained from which the starting material is regenerated even on acidification at 0°. Many experiments were performed but in none of these was there any evidence for the production of a diketo-acid on saponification of ψ-santonin, whereas the diketo-acid (XIII) would be expected from structure (I*a*). All the synthetic butenolides give keto-acids on saponification. One possible explanation could be that on hydrolysis the keto-acid undergoes isomeric change with the formation of the cyclic alcohol (XIV), in the same way that Bergmann and Gierth (*Annalen*, 1926, **448**, 48) found that 2-keto*cyclo*hexanol can exist in

the oxido-form (XV). It is possible that on acidification (XIV) could lactonise and undergo isomeric change with the formation of (I*a*).

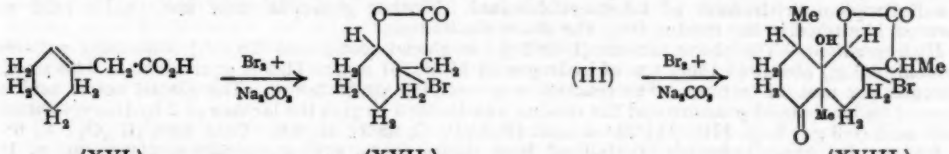
A further difficulty in the way of acceptance of structure (I*a*) lies in the fact that it has been shown that in the butenolides fused to the *cyclo*hexane ring, unless tautomeric change is



(XIII.) (XIV.) (XV.)

impossible as in (VI), the double bond is found in the αβ-position. Why then should ψ-santonin be a βγ-butenolide? We believe that the hydroxyl group is somehow connected with this problem and it may be that structure (I*b*) is more acceptable than (I*a*), but until we have succeeded in synthesising certain hydroxylated butenolides it would be well to withhold further comment.

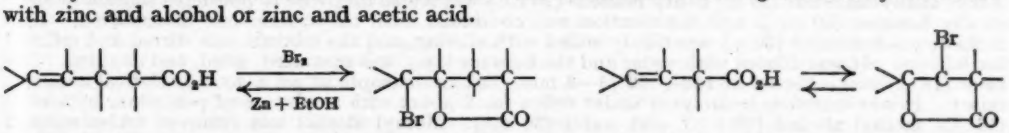
Some Experiments with Dihydro-ψ-santonin.—This compound readily decolourises bromine water, and in quantitative experiments performed under identical conditions with those already described it was found that one mol. of bromine was completely absorbed per mol. of acid in less than 5 minutes. This result is strongly suggestive of a βγ-unsaturated acid. Moreover such βγ-acids readily form bromo-lactones on treatment, in sodium carbonate, with bromine water. Thus Harding, Haworth, and Perkin (*J.*, 1908, **95**, 1963) obtained a bromo-lactone, to which they assigned the structure (XVII), when *cyclo*hex-1-enylacetic acid (XVI) was brominated in sodium carbonate. In a similar manner when dihydro-ψ-santonin was treated in sodium carbonate with bromine water a white crystalline solid was obtained. This was a bromo-lactone, $C_{15}H_{21}O_4Br$, and to this compound by analogy we assign structure (XVIII).



(XVI.) (XVII.) (XVIII.)

The possibility that the bromo-lactone is a β-lactone may be ruled out, since we have shown already that the αβ-double bond is resistant to attack of bromine and the mechanism of addition of hypobromous acid is undoubtedly similar to that of bromine itself.

Such bromo-lactones as those mentioned above should be capable of reduction to the corresponding unsaturated acids. Thus Winterstein and his co-workers (*Z. physiol. Chem.*, 1931, **199**, 25, 37, 46, 56, 64, 75) have shown that βγ- and γδ-unsaturated acids can be converted into crystalline bromo-lactones from which the unsaturated acids are regenerated by reduction with zinc and alcohol or zinc and acetic acid.



When the bromo-lactone (XVIII) was refluxed with zinc dust in alcohol it was smoothly reconverted into dihydro-ψ-santonin. In an analogous manner *cyclo*hex-1-enyl-α-*iso*butyric acid was converted into a bromo-lactone, $C_{10}H_{15}O_2Br$, from which the unsaturated acid was again obtained by reduction with zinc and alcohol.

We consider that the above evidence strongly supports the structure (III) suggested for dihydro-ψ-santonin.

Experimental.

*Lactone of 2-Hydroxy*cyclo*hexylideneacetic Acid* (IV). *2-Keto*cyclo*hexylmalonic Acid.*—Ethyl malonate (63·4 g.) was added dropwise to a stirred and boiling suspension of powdered sodium (9·1 g.) in benzene (300 c.c.) and the reaction was continued until all the sodium had disappeared. The cooled mixture was then slowly treated, with stirring, with 2-chloro*cyclo*hexanone (63 g.). After 1 hour in the cold the mixture was heated on the water-bath and refluxed, with stirring, for 8 hours. It was then cooled and acidified with dilute acetic acid, and the benzene layer was separated, washed with water, and dried. On distillation *ethyl 2-keto*cyclo*hexylmalonate* (49 g.) was collected as a colourless oil, b. p. 150—151°/3 mm. (Found: C, 61·5; H, 7·9. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·8%). This ester was

hydrolysed by heating for 2 hours under reflux with a solution of potassium hydroxide (34 g.) in methyl alcohol (500 c.c.) and water (50 c.c.). Methyl alcohol was then removed and the residue was diluted with water, shaken with charcoal, and filtered. The filtrate was acidified, saturated with ammonium sulphate, and extracted several times with ethyl acetate from which the required 2-keto*cyclo*hexylmalonic acid was obtained (19 g.), m. p. 160°. It crystallised from water as colourless needles, m. p. 168—169° (decomp.). McCrae, Charlesworth, and Alexander (*loc. cit.*) give m. p. 163° (Found: C, 54·1; H, 6·0; equiv., 105·1. Calc. for $C_9H_{12}O_5$: C, 54·0; H, 6·0%; equiv., 100). Its 2:4-*dinitrophenylhydrazone* crystallised from alcohol as yellow needles, m. p. 218—219° (decomp.) (Found: C, 48·0; H, 4·5. $C_{15}H_{16}O_8N_4$ requires C, 47·4; H, 4·2%).

The above acid (19 g.) was gently refluxed for 2 hours with acetic anhydride (80 g.) and the acetic anhydride was then removed under reduced pressure. The residual oil was dissolved in ether, washed several times with sodium hydrogen carbonate solution, dried, and distilled. The product distilled almost completely at 131—133°/3—4 mm. and on cooling it solidified to a mass of colourless needles of (IV), m. p. 29—30° (Found: C, 69·3; H, 7·3. Calc. for $C_8H_{10}O_3$: C, 69·6; H, 7·25%). On hydrolysis with 10% methyl-alcoholic potash the lactone yielded 2-keto*cyclo*hexylacetic acid, m. p. 73°, undepressed by admixture with an authentic specimen prepared by heating 2-keto*cyclo*hexylmalonic acid (cf. McCrae *et al., loc. cit.*) (Found: equiv., 150. Calc. for $C_8H_{12}O_3$: equiv., 156). 2-*Keto*cyclo*hexylacetic acid* 2:4-*dinitrophenylhydrazone* crystallised from dilute alcohol as yellow needles, m. p. 193—194° (Found: C, 50·5; H, 4·8. $C_{14}H_{16}O_6N_4$ requires C, 50·0; H, 4·8%).

Oxidation of the Lactone.—(a) *With neutral potassium permanganate.* The lactone (1·0 g.) in water (10 c.c.) containing magnesium sulphate (3 g.) was slowly treated, with shaking, with 1% permanganate (75 c.c.). The mixture was then further shaken for 30 minutes. It was made alkaline to phenolphthalein and filtered. The filtrate was warmed for 30 minutes on the water-bath and extracted with ether from which unoxidised lactone, m. p. 29—30°, was obtained. The alkaline residue was evaporated to a very small bulk, acidified with sulphuric acid, and extracted many times with ether from which adipic acid (crude, m. p. 140°) was isolated. The aqueous residue was freed from sulphate ions, buffered with sodium acetate, and treated with calcium chloride; calcium oxalate was produced, soluble in hydrochloric acid and capable of reducing acid potassium permanganate.

(b) *With ozone.* The lactone (0·5 g.) in purified chloroform (25 c.c.) was subjected to ozonised oxygen (0·009 g.-mol. O_3/hr.) for 30 minutes. The solvent was then removed in a vacuum at room temperature and the residue was shaken thoroughly with water and left overnight. The solution was treated with sodium carbonate (0·5 g.) and steam distilled. The distillate yielded a 2:4-dinitrophenylhydrazone which on crystallisation from alcohol gave m. p. 231—232° undepressed by an authentic specimen of the 2:4-dinitrophenylhydrazone of 2-keto*cyclo*hexanol. Neither glyoxylic acid nor oxalic acid was, however, identified in the residue from the steam distillation.

Hydrogenation.—The above lactone (1·0002 g.) in glacial acetic acid (20 c.c.) containing palladised charcoal (0·5 g.) absorbed 166·4 c.c. of hydrogen at 15·5°/761 mm. This is equivalent to 0·98 mols. of hydrogen per mol. of lactone. The reaction was complete in 16 hours. The glacial acetic acid was removed under reduced pressure and the residue was distilled to give the lactone of 2-hydroxy*cyclo*hexylacetic acid (0·9 g.), b. p. 110—111°/3—4 mm. (Found: C, 68·3; H, 8·6. Calc. for $C_8H_{12}O_3$: C, 68·6; H, 8·6%). Its *phenylhydrazide* crystallised from dilute acetic acid in colourless plates, m. p. 168° (Found: C, 67·7; H, 8·2. $C_{14}H_{20}O_2N_2$ requires C, 67·7; H, 8·1%). No acid products were isolated from the reduction, and when the reduced lactone was hydrolysed by alkali and the solution acidified it was regenerated unchanged.

When (IV) (0·3070 g.) was hydrogenated in acetic acid (20 c.c.) containing Adams's platinic oxide catalyst (0·05 g.) at 20°/769 mm. hydrogen was rapidly absorbed and absorption was complete (1·17 mols. of hydrogen per mol. lactone) in 30 minutes. When the acetic acid was removed the residue was found to be insoluble in sodium carbonate, and it gave a phenylhydrazide identical with that described above.

*Lactone of 2-Hydroxy*cyclo*hexylidene-α-propionic Acid* (V). *2-Keto*cyclo*hexyl-α-propionic Acid.*—The following method was found to be more convenient than that described by Clemo and Cocker (*loc. cit.*). Ethyl methylmalonate (27 g.) in dry benzene (20 c.c.) was added dropwise to powdered sodium (3·55 g.) in dry benzene (50 c.c.), and the reaction was continued until the sodium had disappeared. Then 2-chloro*cyclo*hexanone (20 g.) was slowly added with stirring, and the mixture was stirred and refluxed for 8 hours. It was diluted with water and the benzene layer was separated, dried, and distilled. The ester (18 g.) was collected at 158—162°/3—4 mm., but all attempts to get a good analytical specimen failed. It was therefore hydrolysed under reflux for 2 hours with a mixture of potassium hydroxide (12 g.), methyl alcohol (90 c.c.), and water (30 c.c.). Methyl alcohol was removed under reduced pressure, and the cooled residue was acidified with dilute sulphuric acid and extracted with ether from which 2-keto*cyclo*hexyl-α-propionic acid (5 g.) was obtained, m. p. 133—134°. It crystallised from water (charcoal) as colourless plates, m. p. 134·5—135·5° (Found: equiv., 172. Calc. for $C_9H_{14}O_3$: equiv., 170). Its 2:4-dinitrophenylhydrazone crystallised from alcohol as yellow needles, m. p. 244° (decomp.) (Found: C, 51·3; H, 5·5. Calc. for $C_{15}H_{18}O_6N_4$: C, 51·4; H, 5·1%).

Lactone (V).—The above keto-acid (17·5 g.) was heated under reflux for 2 hours with acetic anhydride (60 c.c.). Acetic anhydride was removed under reduced pressure and the residue was extracted with ether. The extract was washed several times with sodium hydrogen carbonate solution, dried, and distilled, to give the required lactone as a highly refractive liquid, b. p. 133—134°/3 mm. (Found: C, 70·5; H, 7·8. $C_9H_{12}O_3$ requires C, 71·0; H, 7·9%). This lactone was somewhat less soluble in water than its lower homologue, but it was readily and quantitatively saponified with 5—10% methyl-alcoholic potash to 2-keto*cyclo*hexyl-α-propionic acid, m. p. and mixed m. p. 135°.

Attempted hydrogenation. The above lactone (0·9763 g.) in glacial acetic acid (20 c.c.) containing palladised charcoal (0·5 g.) was hydrogenated at 15°/745 mm. 17·5 C.c. of hydrogen were absorbed in about 15 minutes, and then absorption ceased. Adams's catalyst (0·1 g.) just previously reduced was later introduced and a further 30·0 c.c. of hydrogen was absorbed, but even after further shaking overnight no appreciable further absorption took place. On removal of the acetic acid and alkaline hydrolysis of the residue, 2-keto*cyclo*hexyl-α-propionic acid (0·7 g.), m. p. 135°, was recovered.

2-*Hydroxy*cyclo*hex*-1-*enyl*-α-iso*butyrolactone* (VI; $R_1 = R_2 = Me$).—(*a*) *From* 2-*acetoxy*cyclo*hexanone*. Clean and bright zinc wool (3·2 g.; 2·1 g.-atoms) was added in portions to 40 c.c. of a mixture of 2-acetoxy*cyclo*hexanone (3·5 g.; Bergmann and Gierth, *Annalen*, 1926, **448**, 48), ethyl α-bromo*iso*butyrate (4·4 g.), iodine (0·05 g.), and dry benzene (85 c.c.), and the whole was brought to the boil, under reflux, with stirring. Reaction set in, and after 10 minutes the remainder of the benzene solution was added dropwise to the stirred mixture. Stirring and refluxing were then continued for 3 hours. The mixture was cooled and added to 10% sulphuric acid and ice, and, after shaking, the benzene layer was separated, washed with 5% sodium hydrogen carbonate solution, dried, and distilled, the fraction b. p. 139—140°/6 mm. being collected. This was again distilled and the *ester* collected as a colourless viscous liquid (4·6 g.), b. p. 127—130°/3—4 mm. (Found: C, 62·4; H, 8·9. $C_{14}H_{24}O_5$ requires C, 61·8; H, 8·8%). The ester (3·55 g.) was hydrolysed by heating under reflux for 3 hours with potassium hydroxide (2·5 g.) and methyl alcohol (50 c.c.). Methyl alcohol was removed, and the residue was dissolved in water, clarified with charcoal, and acidified with 20% sulphuric acid. The solution was then saturated with ammonium sulphate and extracted with ether from which a solid, m. p. 69—73°, was obtained. It was crystallised from ligroin (b. p. 40—60°), and the *lactone* of 1 : 2-dihydroxy*cyclo*hexyl-α-*iso*butyric acid (XI) was obtained as colourless needles, m. p. 107—108° (Found: C, 65·6; H, 8·3. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). Attempted dehydration of the ester (3·2 g.) was carried out by boiling for 3 hours with acetic anhydride (6 g.) and fused sodium acetate (3 g.). On hydrolysis of the product only (XI) was obtained. Again dehydration was attempted by heating the ester (2·0 g.) with pyridine (20 c.c.) and phosphoryl chloride (7 c.c.) at 150—160° for 4 hours. The reaction mixture was then cooled and poured into ice and sulphuric acid and the mixture was exhaustively extracted with ether. From the extract a small quantity of oil, b. p. 100—130°/3 mm., was obtained, from which by hydrolysis (XI) was produced. The lactone (XI; 0·5 g.) was heated on the water-bath with 30% sulphuric acid in 50% alcohol (10 c.c.) for 3½ hours. The product was an oil which was immediately saponified with 10% sodium hydroxide and the small amount of acidic product was extracted with ether. It yielded a 2 : 4-dinitrophenylhydrazone which had m. p. 250°, undepressed by that of authentic 2-keto-*cyclo*hexyl-α-*iso*butyric acid prepared as described below (*c*).

(*b*) *From* 2-*carbethoxy*cyclo*hexanone*. 2-Carbethoxy*cyclo*hexanone (13 g.) was added dropwise to sodium ethoxide from sodium (1·76 g.) and alcohol (48 c.c.). The solid sodio-derivative was cooled and with stirring ethyl α-bromo*iso*butyrate (15 g.) was slowly added and the mixture was refluxed for 24 hours. Alcohol was then removed and the residue was diluted with water and extracted with ether, from which by distillation a fraction, b. p. 155—180°/2—3 mm., was obtained. On redistillation a fraction (5·3 g.) was collected at 170—178°/2—3 mm. This fraction was refluxed for 3 hours with a solution of potassium hydroxide (4 g.) in methyl alcohol (50 c.c.), methyl alcohol was distilled off, and the residue, after acidification was saturated with ammonium sulphate and extracted many times with ether. From this extract pimelic acid, m. p. 103—104° (Found: C, 52·5; H, 7·5; equiv., 73·2. Calc. for $C_7H_{12}O_4$: C, 52·5; H, 7·5%; equiv., 80), and another solid product were isolated. The latter consisted of hygroscopic needles. It was strongly acid but gave no carbonyl reactions. It was not investigated further.

(*c*) *From* 1-*hydroxy*cyclo*hexyl*-α-iso*butyric acid*. This compound was previously prepared by Wallach and Mallinson (*loc. cit.*) but experimental details were scanty. We adopted the following procedure. Clean and bright zinc wool (32 g.) was added in five equal portions to a stirred boiling mixture of *cyclo*hexanone (40 g.), ethyl α-bromo*iso*butyrate (80 g.), iodine (0·05 g.), and benzene (150 c.c.). The mixture was heated with stirring for 3 hours, then cooled, poured on crushed ice, and shaken with 20% sulphuric acid (300 c.c.). The benzene layer was removed and the aqueous layer was further extracted with benzene and the combined benzene extracts were dried. The extract was distilled and the fraction, b. p. 134—136°/10—12 mm. (32 g.), collected. This consisted of ethyl 1-hydroxy*cyclo*hexyl-α-*iso*butyrate. The above ester (30 g.) was heated for 2½ hours at 150—160° with freshly fused potassium hydrogen sulphate (60 g.). The mixture was cooled and the paste extracted several times with ether. The ether extract was distilled and the fraction (13 g.), b. p. 130—136°/10—12 mm., collected. This was substantially ethyl *cyclo*hex-1-enyl-α-*iso*butyrate. An earlier fraction (13 g.), b. p. 120—130°/10—12 mm., was the undehydrated ester. A mixture of the unsaturated ester (13 g.), potassium hydroxide (7·2 g.), and methyl alcohol (120 c.c.) was refluxed for 3 hours. The methyl alcohol was distilled off and the residue diluted with water and extracted with ether. The aqueous layer was then clarified with charcoal, acidified, and extracted with ether from which by distillation *cyclo*hex-1-enyl-α-*iso*butyric acid (4·5 g.) was obtained as a viscous liquid, b. p. 154—160°/10—12 mm. It solidified on being kept, and crystallised from dilute alcohol as long colourless needles, m. p. 71—72° (v. Braun and Münch, *Annalen*, 1928, **465**, 52, give m. p. 69—71°). The acid (0·1 g.) in 10% sodium carbonate (20 c.c.) was treated at room temperature with saturated bromine water in excess. The opalescent liquid was then extracted with ether from which an oil was obtained which slowly solidified. It was purified by sublimation in a vacuum and the *bromo-lactone* was obtained as long prisms, m. p. 59—60° (Found: C, 49·2; H, 6·3. $C_{10}H_{15}O_2Br$ requires C, 48·6; H, 6·1%). This lactone had a strong camphoraceous odour; it was insoluble in cold sodium hydroxide but on being warmed with this reagent it rapidly decomposed giving a solution containing sodium bromide.

The above unsaturated acid (13·5 g.) was stirred and gently refluxed with 50% sulphuric acid (135 g.) for 6 hours. The dark gum which was produced on dilution with water was extracted with ether, and the extract was washed with 5% sodium carbonate and dried. On distillation two fractions were obtained: (i) b. p. 50°/10—12 mm. (4 g.), and (ii) b. p. 136—140°/10—12 mm. (4·3 g.). Fraction (i) was distilled at atmospheric pressure and collected at 155—157°. It was undoubtedly 1-*iso*propyl-*cyclo*hexene (Found: C, 86·6; H, 12·3. Calc. for C_9H_{16}: C, 87·1; H, 12·9%). It gave a nitrosochloride which crystallised from benzene–ligroin as needles, m. p. 143—144°. Wallach and Mallinson (*loc. cit.*) give m. p. 129—130° (Found: C, 57·3; H, 8·4. Calc. for $C_9H_{16}ONCl$: C, 56·9; H, 8·4%). Fraction (ii) was the lactone of 2-hydroxy*cyclo*hexyl-α-*iso*butyric acid; it solidified on standing and had m. p. 48°. It was considered to be sufficiently pure for the further stages of the synthesis. The lactone (4·3 g.) was hydrolysed by boiling with sodium hydroxide (2 g.) in water (20 c.c.) for 30 minutes. The clear solution

was treated with a boiling solution of magnesium sulphate (6 g. of the heptahydrate) in water (40 c.c.). It was cooled, shaken thoroughly, and treated dropwise at 0° with bromine (5 g.). The mixture was then shaken for 24 hours, further portions of sodium hydroxide being added at intervals to ensure very slight alkalinity to phenolphthalein. The mixture was acidified and exhaustively extracted with ether, from which, after drying, a dark red solid was obtained. This was dissolved in a slight excess of sodium carbonate solution, boiled with charcoal, and filtered, and the hot solution was acidified with concentrated hydrochloric acid. The buff-coloured acid (2·7 g.) had m. p. 149—150° and was considered sufficiently pure for further work. A portion recrystallised from water (charcoal) was deposited as colourless prisms, m. p. 151½—152°. This was undoubtedly 2-*keto*cyclo*hexyl*-α-iso*butyric acid* (Found: C, 64·6; H, 8·6. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·6%). Its 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as yellow needles, m. p. 255—256° (decomp.) (Found: C, 52·3; H, 6·0. $C_{16}H_{20}O_8N_4$ requires C, 52·7; H, 5·5%). The above keto-acid (2·7 g.) dissolved in acetic anhydride (15 g.) was heated under reflux for 2 hours. The acetic anhydride was then removed under reduced pressure and the residue was extracted with ether. The extract was washed with sodium carbonate, dried, and distilled, and 2-*hydroxy*cyclo*hex*-1-*enyl*-α-iso*butyrolactone* (1·8 g.) was collected at 119—120°/10—11 mm. (Found: C, 71·5; H, 8·3. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%). On alkaline hydrolysis the keto-acid was regenerated.

Hydrogenation of the Lactone (VI; $R_1 = R_2 =$ Me).—When the lactone (0·1996 g.) in glacial acetic acid (10 c.c.) mixed with palladised charcoal (0·2 g.) was submitted to hydrogenation at 16°/755 mm. no hydrogen was absorbed, but in a second experiment when lactone (0·1514 g.) in acetic acid (10 c.c.) mixed with Adams's platinic oxide catalyst (50 mg.) was reduced at 18°/758 mm., 7—8 c.c. of hydrogen were absorbed in 3 minutes and two molecules (43 c.c.) in 15 minutes. The acetic acid was then removed in a vacuum and a solid residue was obtained which was completely soluble in sodium carbonate with effervescence. The alkaline solution was shaken with charcoal, filtered, and acidified to give *cyclo*hexyl-α-*iso*butyric acid as silvery plates, m. p. 77—78°, raised only to 80° on two crystallisations from dilute alcohol. This compound was identical with that obtained when *cyclo*hex-1-enyl-α-*iso*butyric acid (0·2 g.) was hydrogenated in glacial acetic acid (15 c.c.) mixed with Adams's catalyst (0·06 g.) at 15°/751·5 mm. The total absorption, which took 15 minutes to complete, was 28·4 c.c., equivalent to 1 mol. of hydrogen per mol. of unsaturated acid. No hydrogenation took place with palladised charcoal as catalyst.

Attempts to Prepare 1-*Hydroxy*-3 : 4-*dihydronaphthalene*-2-α-iso*butyrolactone*.—The method adopted was the attempted condensation of ethyl α-bromo*iso*butyrate with ethyl 1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylate. α-Tetralone was prepared by the ring closure of γ-phenylbutyric acid with a mixture of phosphoric acid and phosphoric oxide (cf. Birch and Robinson, *J.*, 1945, 582); this method was more economical than the usual one involving the ring closure of γ-phenylbutyryl chloride (*Org. Synth.*, Coll. Vol. II, 569). α-Tetralone was converted into ethyl 1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene-2-glyoxylate by a method similar to that employed by Hückel and Goth (*Ber.*, 1924, **57**, 1288), but decomposition of this compound to give the carboxylate was improved as follows. A mixture of the glyoxylate (7·5 g.) and finely powdered glass (7 g.) was heated in an oil-bath maintained at 190—195° for 2 hours. On cooling, the paste was extracted several times with ether from which the required ester (6 g.) was obtained as a colourless liquid, b. p. 153—155°/2 mm. (Found: C, 71·9; H, 6·5. Calc. for $C_{13}H_{14}O_3$: C, 71·6; H, 6·4%). The keto-ester (11·3 g.) was slowly added to a suspension of finely powdered potassium (2·1 g.) in xylene (50 c.c.) and the mixture was stirred and refluxed until all the potassium had dissolved. The bromo-ester (10·1 g.) was slowly added and the stirred mixture was heated under reflux for 24 hours. It was then cooled and poured into water, and the xylene layer separated and distilled. Five fractions were obtained, namely: (i) 60—70°/3 mm., (ii) 105—145°/3 mm., (iii) 155—160°/3 mm., (iv) 170—175°/3 mm., and (v) 180—185°/3 mm. Of these (i) was unchanged bromo-ester and (iii) was almost pure keto-ester. Fractions (iv) and (v) were separately hydrolysed for 5 hours with 8% methyl alcoholic potassium hydroxide, and from each a very small quantity of solid was obtained which by several crystallisations from dilute alcohol, was obtained as needles, m. p. 191—192° (Found: C, 69·5; H, 4·0%). It did not give a precipitate with 2 : 4-dinitrophenylhydrazine and was recovered unchanged after boiling with acetic anhydride for 2 hours. Its investigation was therefore abandoned.

Experiments with Dihydro-ψ-santonin.—All attempts to reduce dihydro-ψ-santonin in presence of palladised charcoal were unsuccessful, but it can be reduced in presence of Adams's catalyst (cf. Clemo and Cocker, *loc. cit.*).

Bromination. Dihydro-ψ-santonin (0·2 g.) in water (10 c.c.) containing sodium carbonate (0·5 g.) was slowly treated, with stirring, with bromine water (0·12 c.c. of bromine in 15 c.c. of water). On the addition of the first drop of bromine water a white precipitate was formed, and this was ultimately collected. It was washed with 10% sodium carbonate, then with water, and dried. On crystallisation from dilute alcohol the *bromo-lactone* was deposited as colourless prisms, m. p. 180° (decomp.) (Found: C, 52·6; H, 6·15; Br, 22·6. $C_{15}H_{21}O_4Br$ requires C, 52·2; H, 6·1; Br, 23·2%). This compound was readily decomposed on boiling with water yielding a solution containing hydrobromic acid.

Reduction of the bromo-lactone. Bromo-lactone (0·3 g.) in alcohol (5 c.c.) was refluxed with zinc dust (1·0 g.) for 4 hours. The hot mixture was filtered and the filtrate was evaporated to dryness. An oily residue was left and this was rubbed with 10% hydrochloric acid to remove zinc; a solid was thus obtained which, after being washed, was recrystallised from dilute alcohol; it separated as needles (0·2 g.), m. p. 187—188° undepressed with authentic dihydro-ψ-santonin. This compound was again obtained when the bromo-lactone was heated on the water-bath with zinc dust and acetic acid for 3 hours.

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217. *The Kinetics of Aromatic Halogen Substitution. Part III. Iodination by Iodine Chloride.*

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Iodination by iodine chloride of, *e.g.*, acetanilide and anisole, like the corresponding brominations by bromine, shows third-order kinetics in acetic acid solution. When there is steric hindrance to the entry of the iodine atom into the benzene ring, as in pentamethylbenzene and *p*-tolyl methyl ether, there is concomitant iodine chloride-catalysed chlorination, and this has an inducing effect on the iodination. In chlorobenzene solution this side reaction becomes more prominent, occurring with a compound like anisole, for which steric hindrance is not to be expected.

The use of iodine chloride as an iodinating agent has long been known, but its applicability is limited. Chattaway and Constable (*J.*, 1914, **105**, 124) showed that in acetic acid solution, a 90% yield of the *p*-iodo-derivative is obtained from acetanilide. In iodination with iodine chloride the liberated hydrogen chloride combines with the reagent to form $HICl_2$, with the result that the rate falls off rapidly during the course of the reaction, just as in the corresponding brominations owing to HBr_2 formation. This complicates the kinetic interpretation, necessitating measurements of the initial rates for the evaluation of the reaction order. The general conditions of such measurements have been discussed in Part I of this series (*J.*, 1943, 276). The following results were obtained for acetanilide, times (mins.) being shown for 10% iodine chloride absorption in acetic acid.

Temp.	M/20.		M/40.
24°	160	($n = 3{\cdot}3$)	780
50	36	($n = 2{\cdot}6$)	105

The order is approximately 3 at 24° and is less at 50°, an effect similar to that found in the bromination of this compound, for which orders, $n = 3{\cdot}0$ (24°) and $n = 2{\cdot}5$ (50°), were obtained at the same concentrations.

The iodination of anisole in acetic acid is accompanied by a certain amount of simultaneous chlorination. Equimolecular amounts of reactants, M/20, at 24°, ceased to react at 78% halogen absorption owing to the formation of $HICl_2$. To such a solution a slight excess of anisole was added, and dry nitrogen passed through for 15 minutes. This procedure removed hydrogen chloride, but no chlorine, permitting a further gradual 8% halogen absorption, after which only iodine was left. The ratio of iodination to chlorination is therefore approximately 5 : 1, and on adding water to the solution, *p*-iodoanisole, m. p. 50—52°, was precipitated. The contribution of this concurrent chlorination is not sufficient seriously to affect the order of the iodination reaction, and the times, in acetic acid at 24°, indicate third-order kinetics :

	M/20.		M/40.		M/80.
Time ($x = 20$) at 24°	11·8	($n = 3{\cdot}0$)	46·5	($n = 3{\cdot}1$)	216
Time ($x = 20$) at 40°	4·8	($n = 3{\cdot}0$)	19·0	($n = 3{\cdot}0$)	77

Experiments with anisole in relative excess revealed that the reaction was unimolecular with reference to anisole and bimolecular with reference to iodine chloride.

Pentamethylbenzene, which was found to undergo bromination in acetic acid at a rapid rate approximately the same as that for anisole, reacts moderately rapidly with iodine chloride. With this compound a steric effect is to be expected, as the approach of the large iodine atom is hindered by the *ortho*-methyl groups. This reveals itself in the sense that the alternative chlorine substitution makes a greater contribution than in the reaction with anisole, where there is no steric hindrance. In M/20-solution in acetic acid at 24° there is 80% halogen absorption, corresponding with the relative contributions, iodination : chlorination = 3 : 1. Rate measurements show predominantly third-order kinetics in the experimental concentration range :

	M/40.		M/80.
Time ($x = 10$)	26	($n = 2{\cdot}9$)	95

In *p*-tolyl methyl ether steric hindrance to the entry of the large iodine atom into the *o*-position is also to be expected, and with M/20-reactants in acetic acid at 24° the iodine chloride substitution stops at ~67% halogen absorption, corresponding with equal contributions of iodination and chlorination; disturbed third-order kinetics are observed :

	M/20.		M/40.		M/80.
Time ($x = 20$)	86	($n = 3{\cdot}3$)	420	($n = 2{\cdot}7$)	1390

A summary of these iodine chloride reactions is now given:

	Acetanilide.	Anisole.	Pentamethylbenzene.	*p*-Tolyl methyl ether.
Concurrent chlorination ...	10%	20%	30%	50%
Relative rates, Br_2/ICl	950 : 1	350 : 1	150 : 1	70 : 1

Instead of the total rate of halogenation with iodine chloride becoming less (as compared with bromination) when there is steric hindrance, the reverse effect is observed. The alternative chlorine substitution, which is catalysed by iodine chloride, apparently exerts an inducing effect on the iodination by this reagent, and this becomes more considerable as the relative contribution of the chlorination increases. Other examples of induction in halogenation reactions have been reported (cf. *J.*, 1945, 509). On changing to chlorobenzene as solvent, the tendency for iodine chloride halogenation to proceed by the chlorination route becomes more pronounced, even when there is no steric hindrance; *e.g.*, for anisole the contribution of the chlorination is 50%. Correspondingly, there is an increase in the velocity of the reaction, the relative rates, Br_2 to ICl, for anisole in chlorobenzene being 5 : 1 (in acetic acid solution the ratio is 350 : 1). This concurrent halogenation observed with iodine chloride should be still more pronounced with iodine bromide, as this compound is more dissociated than the chloride. According to Militzer (*J. Amer. Chem. Soc.*, 1938, **60**, 256), phenol in carbon tetrachloride solution is exclusively brominated by iodine bromide. It is not, however, necessary to assume that this reaction proceeds according to the scheme $XH + IBr \longrightarrow XBr + HI$; $HI + IBr \longrightarrow I_2 + HBr$, for a mechanism involving iodine bromide-catalysed bromination will explain the experimental result.

The iodination of aromatic compounds by iodine chloride is analogous, not only to bromine substitution, but also to iodine chloride and bromine addition to unsaturated compounds. In acetic acid solution in the concentration region M/40, all four reactions show third-order kinetics, the order being reduced on rise in temperature owing to the incursion of a bimolecular reaction. It is concluded that the reaction mechanisms are similar (cf. *J.*, 1943, 279), taking place for iodination according to the scheme:

$$XH + ICl \underset{2}{\overset{1}{\rightleftharpoons}} XH,ICl; \quad XH,ICl + ICl \xrightarrow{3} \overset{+}{X}HI + \overset{-}{I}Cl_2 \xrightarrow{\text{rapid}} XI + HICl_2$$

and for third-order kinetics

$$d[XI]/dt = (k_1k_3/k_2)[XH][ICl]^2.$$

Experimental.

The compounds used were: anisole, b. p. 154·5°/760 mm.; *p*-tolyl methyl ether, b. p. 179°/760 mm.; acetanilide, m. p. 113·5°; pentamethylbenzene, m. p. 53·5°. The general technique was as previously described, the reactions being carried out with darkened bottles in a room with dim illumination. At 24° the iodine chloride solutions in acetic acid were found to be stable during the time of a reaction, but at higher temperatures there was a slight decrease in titre, necessitating a small correction. Herewith a typical set of measurements:

10 Ml. anisole, M/40 + ICl, M/40; HOAc, 50°; 1 ml. samples titrated with KI and 0·01N-$Na_2S_2O_3$.

Time (mins.)	0	10	15	20	30	50
Titre (ml.)	4·98	4·62	4·46	4·25	3·98	3·62
Zero titre (ml.)	—	4·98	4·97	4·97	4·96	4·95

From the curve, $x = 10$, $t = 15$; second expt., $x = 10$, $t = 14$.

Experiments to determine relative contributions of anisole and iodine chloride in acetic acid at 24°; times (mins.), $x = 10$; A, M + ICl, M/20, $t = 0{\cdot}60$; A, M/2 + ICl, M/40, $t = 3{\cdot}0$; A, M/4 + ICl, M/40, $t = 3{\cdot}5$; A, M/4 + ICl, M/80, $t = 8{\cdot}0$: these gave n (anisole) 1·2, n (ICl) 2·2. The remaining measurements have been quoted in the text.

Victoria University College, Wellington, N.Z. [*Received, November 21st*, 1946.]

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218. *The Kinetics of Halogen Addition to Unsaturated Compounds. Part XII. Iodine Catalysis of Chlorine and Bromine Addition to Ethyl Cinnamate.*

By H. D. C. Waters, A. R. Caverhill, and P. W. Robertson.

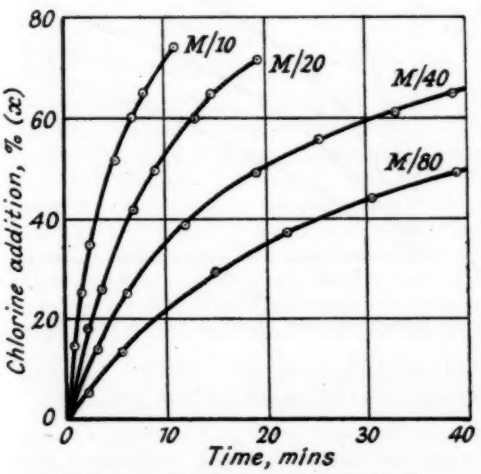
Iodine-catalysed addition of chlorine to ethyl cinnamate in carbon tetrachloride solution proceeds according to the expression $-d[Cl_2]/dt = k[A][Cl_2][ICl]$, and in the corresponding bromine reaction, $-d[Br_2]/dt = k[A][Br_2]^2[IBr]$. At higher concentrations of added iodine,

the order for the chloride and the bromide becomes greater than unity. In the polar solvents chloroform and *o*-dichlorobenzene, the overall rate is one order less than in carbon tetrachloride, as for uncatalysed bromine addition. A general theory is proposed to explain the phenomenon of *trans*-halogen addition with inversion.

THE influence of iodine as a catalyst for bromine addition has long been recognised (Hertz and Mylius, *Ber.*, 1906, **39**, 3816; Bruner and Fischler, *A.*, 1914, ii, 260), but such rate measurements as have been made are insufficient to establish the kinetics of the reaction. Although iodine is known to catalyse chlorine addition to unsaturated compounds, there appears to be no record of any kinetic investigation of such reactions. However, Slator (*J.*, 1903, **83**, 729) has studied the kinetics of the reaction, $C_6H_6 + Cl_2$, in benzene as a solvent or diluted with carbon tetrachloride, with added iodine. The reaction proceeds with 70% substitution and 30% chlorine addition at a rate given by the expression, $-d[Cl_2]/dt = k[A][Cl_2][ICl]^2$, but the reaction was examined over only a limited iodine chloride concentration range.

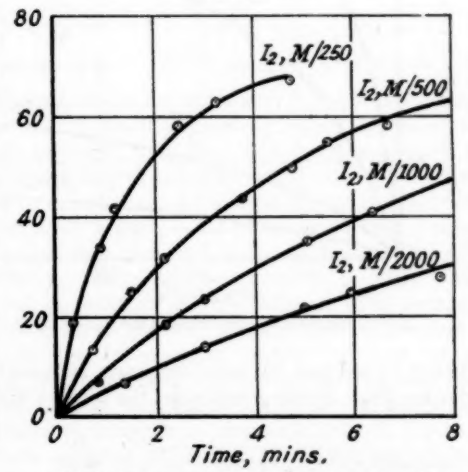
Just as the chlorination of benzene does not proceed in the absence of iodine, chlorine adds to ethyl cinnamate in dry carbon tetrachloride at a rate too slow to be measured, but with a small amount of added iodine the change goes rapidly to completion. At the end of the reaction the original amount of iodine is left, as is indicated by tintometric observation or titration of the

FIG. 1.



Ethyl cinnamate–chlorine, with I_2, M/1000.

FIG. 2.



Ethyl cinnamate–chlorine, both M/20, *with* I_2.

residual iodine. The kinetics of the reaction can be conveniently studied by rate determinations (*a*) with reactants, $A + Cl_2$, constant, and different amounts of iodine, or (*b*) with iodine constant and varying initial concentrations of $A + Cl_2$. The results of these experiments are shown in Figs. 1 and 2, the measurements being made in dry carbon tetrachloride under nitrogen at 24°.

The average orders, $x = 10$ to $x = 50$, for $A + Cl_2$ (Fig. 1) are: M/10—M/20, $n = 2{\cdot}0$; M/20—M/40, $n = 2{\cdot}0$; M/40—M/80, $n = 2{\cdot}0$. The reaction is thus bimolecular with respect to $A + Cl_2$, and the constancy of the bimolecular coefficients during the separate runs indicates the absence of autocatalytic disturbances. This is shown by a typical measurement, in carbon tetrachloride at 24°:

x	10	20	30	40	50
k_2 (reactants M/20, I_2 M/1000)	2·1	2·1	2·1	2·2	2·2

The average values of t_1/t_2 with different amounts of added iodine (Fig. 2) are: M/2000—M/1000, 2·0; M/1000—M/500, 2·0; M/500—M/250, 2·4. On further addition of iodine the initial rates become too rapid for accurate measurements, but reach a maximum when the iodine chloride concentration is approximately equal to that of the chlorine, and then diminish.

The iodine is present almost entirely as chloride, and when its amount is small it does not appreciably alter the chlorine concentration, so these measurements are in accord with the rate expression

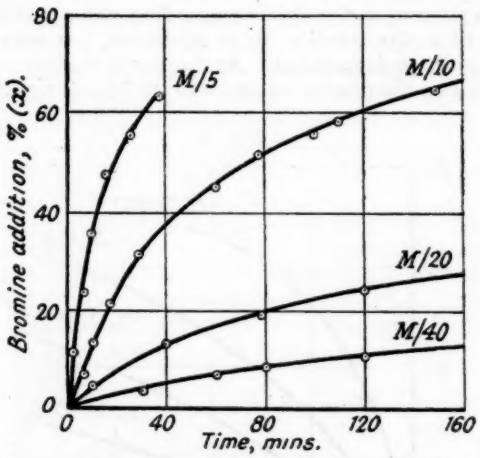
$$-d[Cl_2]/dt = k[A][Cl_2][ICl]$$

The increase in order with respect to iodine, when its amount becomes more considerable, will be discussed later.

The reaction between ethyl cinnamate and bromine in carbon tetrachloride (in nitrogen at 24°) was found to be not accurately reproducible under the conditions of the experiments, a result possibly due to the sensitiveness of this reaction to oxygen (cf. Bauer and Daniels, *J. Amer. Chem. Soc.*, 1934, **56**, 378). Added iodine caused a very considerable acceleration of the rate, and the measurements, now found to be reproducible, were made by varying separately A + Br_2, and I_2 (Figs. 3 and 4).

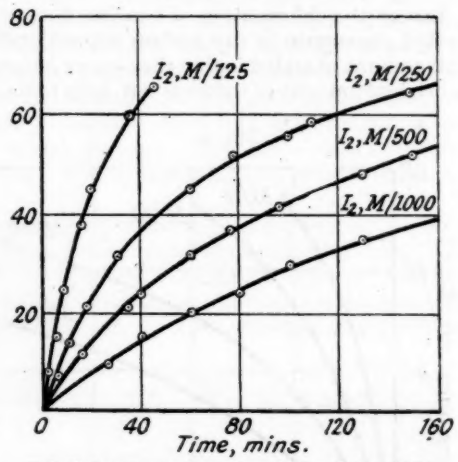
The difference in appearance between Figs. 1 and 3 is due to the fact that bromination is a higher-order reaction than chlorination. The average orders, $x = 20$ to $x = 50$, for A + Br_2, are: M/5—M/10, $n = 2{\cdot}9$; M/10—M/20, $n = 2{\cdot}9$; M/20—M/40, $n = 3{\cdot}0$. Special experiments,

FIG. 3.



Ethyl cinnamate–bromine, with I_2, M/250.

FIG. 4.



Ethyl cinnamate–bromine, both M/10, *with* I_2.

A being varied and Br_2 kept constant, showed that the reaction was first order for A and second order for Br_2. Correspondingly, the bimolecular coefficients fall as the reaction proceeds:

x	10	20	30	40	50	60
k_2 (reactants M/10, I_2 M/500)	0·16	0·155	0·15	0·145	0·135	0·125

The effect of varying the amount of added iodine is shown in Fig. 4, the average t_1/t_2 ratios being: M/1000—M/500, 1·9; M/500—M/250, $n = 1{\cdot}95$; M/250—M/125, 2·7. As for the iodine-catalysed additions of chlorine, the order with respect to iodine is constant for low concentrations of added iodine, and subsequently increases. Iodine with bromine in carbon tetrachloride solution is almost entirely present as IBr, so these results correspond, for small amounts of iodine bromide, with the rate expression

$$-\mathrm{d}[\mathrm{Br_2}]/\mathrm{d}t = k[\mathrm{A}][\mathrm{Br_2}]^2[\mathrm{IBr}]$$

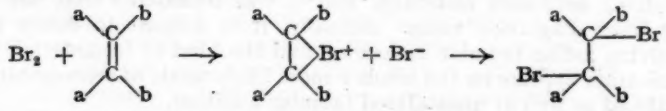
In polar aprotic solvents such as chloroform and *o*-dichlorobenzene, addition of bromine shows third-order kinetics (*J.*, 1945, 509). Added iodine in these solvents causes a relatively smaller catalysis than in carbon tetrachloride, and for small amounts of iodine the rate is given by the expression

$$-\mathrm{d}[\mathrm{Br_2}]/\mathrm{d}t = k[\mathrm{A}][\mathrm{Br_2}][\mathrm{IBr}]$$

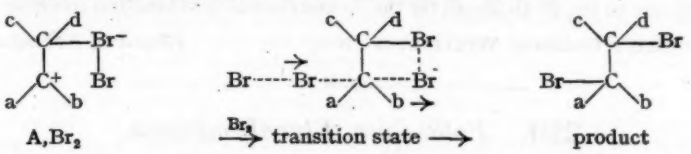
The iodine-catalysed addition of bromine to allyl benzoate in carbon tetrachloride has also been examined, with reactants M/10 and M/20, and iodine M/500 and M/1000. The average orders obtained were A + Br_2, $n = 2{\cdot}8$; IBr, $n = 1{\cdot}3$, so for this compound also the catalysed reaction can be regarded as a fourth-order reaction with one or more molecules of bromine replaced by iodine bromide. With greater amounts of added catalyst, the order for iodine bromide increases, but the reaction becomes too rapid for accurate measurement.

The addition of halogen to ethylenic compounds is a two-stage process, and to explain the

trans-addition with inversion that takes place, Roberts and Kimball (*J. Amer. Chem. Soc.*, 1937, **59**, 947) have proposed the mechanism

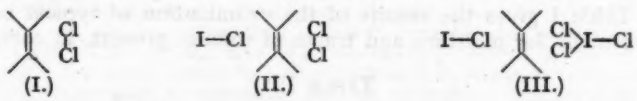


The discovery that addition of bromine may take place by a termolecular mechanism (*J.*, 1937, 335) was not inconsistent with this mode of formulation, as the result could be explained by the reaction proceeding: $A + Br_2 \longrightarrow A,Br_2 \xrightarrow{Br_2} ABr^+ + Br_3^- \longrightarrow ABrBr + Br_2$ (*J.*, 1943, 276). There are, however, certain formalistic difficulties in connection with Roberts and Kimball's theory. The Br^- released in the first stage must move to the reverse side of the positive ion to complete the process, and the model of the transition state reveals a condition of considerable strain. An alternative mechanism is now proposed, according to which the initial addition compound forms a four-atom ring (in which the strain is less than in a three-atom ring) and the change is completed by a second molecule of bromine:

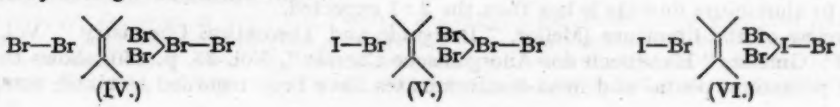


The formation of A,Br_2 is due to the electrophilic attack by Br_2 on A, and A,Br_2 is represented by one of its possible resonance structures. The dotted lines in the diagram of the transition state indicate bond lengths intermediate between covalent and ionic bonds, as suggested by Dostrovsky, Hughes, and Ingold (*J.*, 1946, 173), and the arrows show the direction of the movement of the bromine atoms. The model thus constructed fulfils the requisite conditions for minimum strain, the bonds C–C, C–a, and C–b all being in one plane, and the direction Br–C–Br at right angles to this plane. The criticism may be made, however, that with such a mechanism there should be a possibility of *cis*-addition also, and in fact this is actually found, more extensively indeed than suggested in general in writings on this subject. For instance, Liebermann and Finkenbeiner (*Ber.*, 1895, **27**, 2235) have shown that addition of chlorine to cinnamic acid in the dark in carbon tetrachloride takes place almost entirely by the *cis*-mechanism, whereas in the light the high m. p. isomer formed by *trans*-addition is obtained. No reference was made to the drying of the solvent, so the reaction appears to have been catalysed by water. In the corresponding addition of bromine to cinnamic acid in the same solvent, in the dark there is 37% *cis*-addition, which becomes reduced to 13% when the reaction takes place in light (Michael, *Ber.*, 1901, **34**, 3663). When steric hindrance to addition becomes considerable, *e.g.*, in *o*-nitrostilbene, addition of bromine may take place preferentially by the *cis*-mechanism (Peiffer, *Ber.*, 1915, **48**, 1051).

With a small amount of added iodine we find that addition of chlorine to cinnamic acid, in the dark, takes place with the formation chiefly of the *trans*-addition product. These observations suggest the following modes of reaction mechanism for addition of chlorine to ethyl cinnamate: (I), no iodine, *cis*; (II), a small amount of iodine, *trans*; (III), a larger amount of iodine, *trans*, the iodine trichloride being represented by one of its possible resonance structures.



With the higher-order addition of bromine to ethyl cinnamate the process becomes more complicated, one or two molecules of bromine being replaced in the catalysed reactions by iodine bromide. This is illustrated by the following representations: (IV), fourth-order addition of bromine; (V), the same reaction catalysed by a small amount of iodine; and (VI), catalysed by a larger amount of iodine.



It was proposed (de la Mare, Scott, and Robertson, *J.*, 1945, 509) that the high-order bromine additions in the non-polar solvent carbon tetrachloride might be explained by a chain mechanism involving activated molecules, and it was considered that the iodine-catalysed reactions might have diagnostic value. Actually, it is difficult to devise a suitable chain mechanism involving iodine bromide molecules, and the kind of formulation suggested in the present communication appears on the whole a more likely mode of representation than a chain reaction for catalysed as well as uncatalysed bromine addition.

Experimental.

The materials and method were as previously described (*J.*, 1945, 511) except that chloramine-T was used instead of iodine in the back titration. Herewith the details of one of the measurements:

Ethyl cinnamate, M/20 + Cl_2, M/20 + I_2, M/500 in CCl_4, at 24°.

Time (mins.)	0·88	1·80	2·73	4·80	9·80	12·20
Titre	1·55	1·98	2·34	2·77	3·36	3·61
Back titre	0·84	0·85	0·86	0·88	0·94	0·96
Cl_2 absorption, %	19	30	38	50	65	71

Our thanks are due to Mr. B. B. Marsh for the measurements in chloroform solution.

Victoria University College, Wellington, N.Z. [*Received, November 21st*, 1946.]

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219. *Potassium Fluoaluminates.*

By F. A. Paine and J. Pearson.

The chemical composition of potassium cryolite, the synthetic analogue of the naturally-occurring (sodium) cryolite, does not correspond to the theoretical K_3AlF_6, and certain manufactured batches have been found to be abnormally acid. Preliminary experiments had indicated that the salt was not stable in water; it was therefore desirable that the chemistry of the double fluorides of potassium and aluminium should be studied more fully, and the effect of water on potassium cryolite elucidated. Under normal conditions of manufacture, from aluminium and potassium fluorides or potassium hydroxide and "hexafluoaluminic acid" in aqueous solution, it is impossible to prepare a stable material corresponding to the true potassium hexafluoaluminate. A well-defined pentafluoaluminate, K_2AlF_5, has been shown to exist, and evidence has been obtained for the existence also of a tetrafluoaluminate, $KAlF_4$. When it is expected that the hexafluoaluminate would be formed, there usually results a material in which the molecular ratio of potassium fluoride to aluminium fluoride is slightly less than 3 : 1. This is in agreement with some recently published work. The effect of water upon potassium cryolite has been shown to be, first, dissociation of the double salt into potassium fluoride and potassium pentafluoaluminate, followed by solution of the latter if the concentration of potassium fluoride in the aqueous phase is less than 0·15%. The concentration of potassium fluoride necessary to inhibit dissociation of potassium cryolite is of the order of 0·55%. The high acidities associated with some batches are to be attributed to the presence of an acid salt and not to hydrolytic effects.

During the examination of commercially prepared samples of potassium cryolite, nominally K_3AlF_6, it was found that the potassium contents were much lower, and the aluminium contents much higher, than those calculated. In view of this discrepancy, a review was made of the possible methods of analysing such a substance, and many of them were tried with a view to ascertain whether the unexpected values were the result of unsuitable procedures. Since considerable significance has been attached to the results finally obtained, this review is given in an appendix. Table I gives the results of the examination of typical batches, in which allowance has been made for moisture and traces of sodium present, in comparison with the

Table I.

Sample	1.	2.	3.	4.	5.	6.	Calc., %.
Potassium	43·5	43·6	44·0	44·2	44·5	44·3	45·4
Aluminium	11·1	11·3	11·3	11·3	11·4	11·1	10·5
Fluorine	45·4	45·1	44·7	44·5	44·1	44·6	44·1

expected proportions. From the figures it will be seen that the molecular ratio of potassium fluoride to aluminium fluoride is less than the 3 : 1 expected.

A review of the literature (Mellor, "Inorganic and Theoretical Chemistry", Vol. V, pp. 306, 307; Gmelin, "Handbuch der Anorganische Chemie", Vol. 35, p. 450) shows that until recently potassium penta- and hexa-fluoaluminates have been regarded as stable compounds,

slightly soluble in water, containing potassium and aluminium fluorides in the molecular ratios 2 : 1 and 3 : 1, respectively. Apart from the relative proportions of water of crystallisation present in the salts, there had been no suggestion that any differences existed between the fluoaluminates prepared by melting together the components and those obtained by precipitation from aqueous solutions. During the course of the present investigation, a paper appeared (Brosset, *Chem. Abs.*, **1943**, **37**, 13), demonstrating from crystallographic studies that while potassium penta-fluoaluminate is first formed on adding potassium fluoride to solutions containing aluminium and fluoride ions, the compound produced in the presence of excess of potassium fluoride is not K_3AlF_6 but $K_{3-x}AlF_{6-x}, xH_2O$, *i.e.*, potassium cryolite in which part of the potassium fluoride in the crystal lattice has been replaced by water. Brosset (*loc. cit.*) states that the only stable compounds obtainable by mixing aqueous solutions are K_2AlF_5 and $K_{2\cdot8}AlF_{5\cdot8}$.

Experimental.

In order to test the truth of Brosset's statement, potassium aluminium fluorides were prepared under carefully controlled conditions, and the resulting materials analysed by the methods detailed in the appendix. As a confirmation, conductometric titrations of aluminium fluoride with potassium fluoride in aqueous solution were conducted in the hope that these would reveal the existence of definite compound formation. These experiments are described below. Although the majority of samples of commerical potassium cryolite examined were essentially neutral in reaction, some were found to be abnormally acid, in that their suspensions in water required considerable additions (up to 60 mg. of potassium hydroxide per g. of solid) to render them neutral. The cause of this acidity has also been investigated. It had been anticipated, by analogy with sodium cryolite, that the solubility of potassium cryolite would be very low; reference may be found (Mellor, *op. cit.*) to figures quoted as solubilities of potassium cryolite, and as nothing is said to the contrary, it must be assumed that these refer to what were believed to be true solutions of the cryolite. It was found, however, that in certain circumstances, up to 22% by weight of potassium cryolite could be extracted by water, and qualitative and quantitative tests have indicated that this extractable material is potassium fluoride. In fact, an instance was brought to the authors' notice, in which the high solubility of potassium cryolite was explained on the assumption that the material consisted, not of the double salt, but of a mechanical mixture of the two components, from which water dissolved the more soluble potassium fluoride. In view of the fact that potassium cryolite is normally prepared from aqueous solution, it was decided to investigate fully the action of water on the compound. The results are reported later.

Except in the analytical procedures, it was found necessary to use paraffin-waxed glass or platinum vessels, since many of the reagents employed dissolved glass, etc., to an inconvenient extent.

Preparation of Potassium Fluoaluminates.—(i) *From potassium aluminate and hydrofluoric acid.* Solutions were prepared of potassium aluminate in potassium hydroxide in which the molar ratios of potassium to aluminium were 3 : 1 and 2 : 1. To avoid the presence of other anions, the solutions were made by dissolving weighed amounts of pure aluminium foil in standardised potassium hydroxide. These solutions were titrated with hydrofluoric acid, and the end-points determined potentiometrically with a calomel–antimony electrode combination. As would be expected, the end-points corresponded with the production of K_3AlF_6 and K_2AlF_5, since the potential of the antimony–antimony oxide electrode was influenced only by the hydrogen-ion concentration of the systems. The precipitated solid phases were filtered off, washed with the minimum of cold water, dried, and analysed. The constitutions corresponded to the empirical formulæ $K_{2\cdot9}AlF_{5\cdot9}$ and $K_{1\cdot9}AlF_{6\cdot6}$, respectively. This indicates that although K_3AlF_6 and K_2AlF_5 may have been formed initially, the hexafluoaluminate after brief washing had lost potassium fluoride, whilst the pentafluoaluminate had absorbed, from the finally acid solution, some hydrofluoric acid which had not been removed by washing and drying.

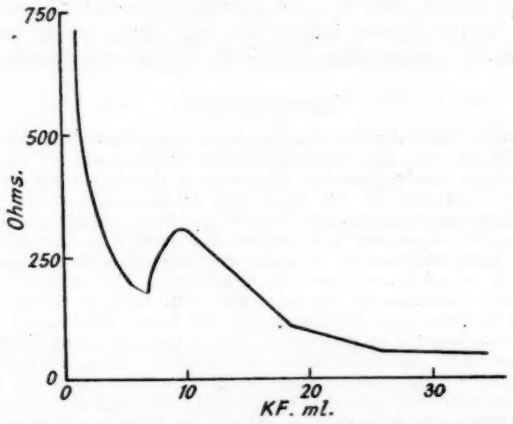
A solution of potassium aluminate (K : Al = 3 : 1) was neutralised with hydrofluoric acid, the potential of the antimony electrode then having a value corresponding to the middle of the potential–volume curve found in the first titration. This potential corresponded very closely with the change-point of methyl-red indicator. Similarly, hydrofluoric acid was neutralised with potassium aluminate. Finally, the aluminate was slightly over-neutralised with the acid. The solid phases produced in each case were filtered off, washed briefly, and dried. 1 G. of each was stirred with 100 ml. of cold water and titrated with N/20-potassium hydroxide solution, the end-points being determined potentiometrically. The acidities of the samples were found to correspond to 0·8, 2·7, and 56·8 mg. of potassium hydroxide per g., respectively. This indicates that in the presence of excess of hydrofluoric acid, potassium cryolite absorbs acid and does not readily part with it. This is probably due to the formation of a small proportion of an acid salt. This acid salt may be considered to be formed by the replacement of part of the potassium fluoride in the crystal lattice by hydrofluoric acid, in the same manner as Brosset (*loc. cit.*) has suggested for the replacement of potassium fluoride by water. The acidities observed in some commercial batches of potassium cryolite are thus to be ascribed to the presence of an acid salt, produced by the addition of slight excess of hydrofluoric acid, and not to hydrolysis. It has been found that a solution of aluminium fluoride in water is not acid.

(ii) *From potassium hydroxide and "hexafluoaluminic acid".* Addition of potassium hydroxide to "hexafluoaluminic acid" (a solution of aluminium fluoride or hydroxide in hydrofluoric acid in the correct proportions) and *vice versa* produced solids having properties, chemical and physical, identical with those of the products obtained above.

Conductometric Titrations of Potassium Fluoride and Aluminium Fluoride.—A saturated solution of aluminium fluoride in water was titrated with aqueous potassium fluoride and the conductivity of the aqueous phase determined when equilibrium had been established after each addition of titrant. Cell-resistance (*i.e.*, reciprocal of conductivity) was actually measured and plotted against volume of

potassium fluoride. The concentration of potassium fluoride was chosen so that the amount added made no significant change in the total volume. A typical curve obtained in this way is shown in Fig. 1. At the stage corresponding to 7·0 ml., precipitation of solid phase commenced, and the sudden rise in resistance at that point is to be attributed to the deposition of salt and not to the formation of a compound. The breaks at 9·3, 18·65, and 26·05 ml. correspond to the formation of $KAlF_4$, K_2AlF_5, and $K_{2\cdot8}AlF_{5\cdot8}$ respectively. This is in agreement with Brosset's work. It is noteworthy that Russian workers have examined synthetic and natural cryolite. Tananaev and Lelchak (*Compt. rend. Acad. Sci. U.R.S.S.*, 1943, XLI, **3**, 144) report that the ratio $NaF : AlF_3$ for Greenland cryolite is in the range 2·7—2·8. They

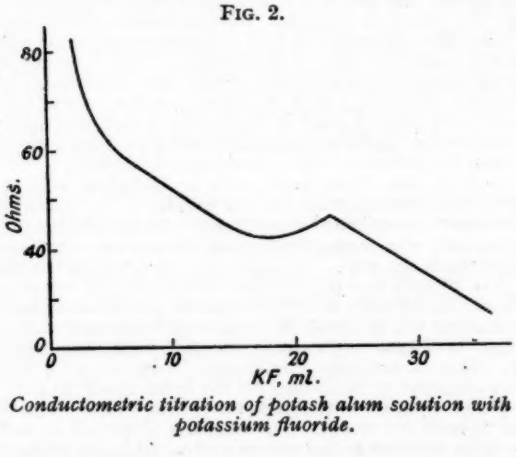
FIG. 1.



Conductometric titration of aluminium fluoride solution with potassium fluoride.

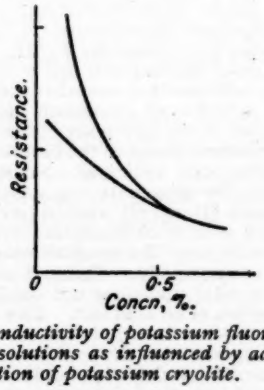
suggest a formula, for the natural and synthetic material, of $11NaF,4AlF_3$, which corresponds to $Na_{3\cdot75}AlF_{5\cdot75}$. Yatlow (*J. Gen. Chem. Russia*, 1937, **7**, 2439) states that sodium cryolite is formed as a result of a reaction between the tetrafluoaluminate, yielded initially by solutions of sodium fluoride and aluminium fluoride, and sodium fluoride. As the proportion of sodium fluoride is increased, the ratio of NaF to AlF_3 in the composition of the precipitate increases from 1 to 2·8. Yatlow has demonstrated the existence of sodium tetra- and penta-fluoaluminates, but states that attempts to synthesise cryolite from aqueous solutions yielded a material of the composition $2\cdot7—2\cdot8NaF,AlF_3$. The analogy with potassium fluoaluminates is thus complete.

FIG. 2.



Conductometric titration of potash alum solution with potassium fluoride.

FIG. 3.



Conductivity of potassium fluoride solutions as influenced by addition of potassium cryolite.

No evidence was found for the formation of the hexafluoaluminate when an aqueous solution of potash alum was titrated with potassium fluoride (see Fig. 2), the only significant break in the curve, at 23·2 ml., corresponding to formation of potassium pentafluoaluminate. After the addition of 18 ml. of potassium fluoride solution, solid commenced to separate; the subsequent rise in resistance is to be attributed to this fact. This observation is not in accord with that of Berzelius (*Pogg. Ann.*, 1824, **1**, 43) that potassium cryolite is formed from potash alum in the presence of excess of potassium fluoride. This point requires further examination, but it is of interest that a commercially prepared material, reputed to be potassium cryolite and made from potash alum and potassium fluoride, was found to consist of the hydrated pentafluoaluminate, K_2AlF_5,H_2O.

The Effect of Water on Potassium Fluoaluminates.—A suspension of potassium cryolite (5 g. in 87·5 ml. of distilled water) was kept at 35° and stirred continuously, with precautions against loss by evaporation. At hourly intervals portions of the suspension were withdrawn, the solid phase removed, and the solution analysed. In every instance the only compound in solution was potassium fluoride. Its concentration increased gradually with time, until after about 6 hours it had become constant. At this stage there was present in every 10 ml. of solution 0·063 g. of potassium fluoride, *i.e.*, a 0·63% solution of potassium fluoride inhibited further dissociation of the hexafluoaluminate to pentafluoaluminate and fluoride.

The conductivities of solutions of potassium fluoride of various concentrations were determined. To fixed volumes of these solutions was added a standard weight of potassium cryolite (two typical commercial materials, $K_{3\cdot7-2\cdot8}AlF_{5\cdot7-5\cdot8}$ were used). The liquid was stirred until no further change in conductivity occurred. The initial and final conductivities (as resistance of a nominal volume of solution) were plotted against the concentration of the original solutions. The curves for the two samples were identical and are shown in Fig. 3. It will be seen that the two branches of the graph merge at a concentration of 0·55 to 0·60%. Since at concentrations below 0·55% the conductivity of a potassium fluoride solution was increased by the addition of potassium cryolite, it follows that dissociation of the cryolite had occurred. At concentrations of 0·60% and above, no alteration in conductivity was observed; no dissociation of the cryolite had taken place. This value for the inhibiting concentration is in good agreement with that found by analysing aqueous extracts; the conductivity measurements were carried out at 20° as against 35° used in the extraction method.

The above-mentioned samples of potassium cryolite and a sample of anhydrous potassium pentafluoaluminate were used to study further the effect of water. 5 G. of each were suspended in 500 ml. of distilled water and shaken at room temperature until equilibrium was reached. The solid residues were removed and dried. The clear solutions and portions of the solids were analysed. 3 G. of the remaining solids were each suspended in 300 ml. of water and treated as above. The first extraction with water removed from each of the cryolites approximately 22% of potassium fluoride and left a residue with a composition approximating to K_2AlF_5. The first aqueous extraction of the potassium pentafluoaluminate removed only 13·3%, and this was found to be of a composition identical with that of the starting material and of the solid residue. The second extraction removed from each sample 13·2% of pentafluoaluminate, leaving a solid of the same composition. It will thus be seen that the action of water on potassium cryolite is to dissociate and dissolve away potassium fluoride and then to take into solution the pentafluoaluminate. Experiments conducted with solutions of various concentrations of potassium fluoride showed that the concentration required to prevent the solution of the pentafluoaluminate is about 0·15%, *i.e.*, slightly less than the 0·22% resulting from the first water-extraction of the cryolite samples.

Appendix.

Analysis of Potassium Fluoaluminates.—(i) *Potassium.* Any method which involves preliminary separation of aluminium with ammonia or ammonium salts, etc., is liable to give low results owing to losses by adsorption on the precipitated alumina, by spitting during evaporation of solutions to dryness, and by decrepitation during heating to expel ammonium salts. Estimation as perchlorate, without separation of aluminium, avoids these losses, and has been found to give results in general higher than those obtained when potassium is estimated as sulphate, a method subject to the above-mentioned disadvantages. Some comparative figures are:

Sample	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*f*)
K, % (determined as K_2SO_4)	42·9	42·5	43·2	43·5	43·5	43·9
K, % (,, $KClO_4$)	43·4	43·8	43·9	43·8	43·5	44·1

(ii) *Aluminium.* Time is saved if aluminium is determined in the solution as used for the potassium estimation. This can be accomplished by precipitation with 8-hydroxyquinoline. Results are identical with those obtained when the aluminium is estimated as alumina; the use of oxine is to be preferred since the aluminium content of the "oxinate" is much smaller than that of alumina, and accidental impurities in the precipitate are of less importance.

(iii) *Fluorine.* Various modifications of the method involving titration with thorium nitrate have been examined. All suffer from the drawback that the end-point of the titration, using sodium alizarinsulphonate as indicator, may be uncertain and difficult to assess, though in the hands of an experienced operator accurate results are obtainable. The estimation as lead chlorofluoride is simpler; the distillation is easy to control, the weight of the sample taken is fairly large, and the estimation may be finished gravimetrically or volumetrically as desired, identical results being obtained by either method. Volumetric estimation was not employed in view of the consumption of silver nitrate. It should be noted that preliminary melting of the material with fusion mixture, as recommended by certain authorities, is not only unnecessary, but leads, in fact, to low results, as shown by the following figures:

F, % with fusion	44·6	44·0	44·3
F, % without fusion	45·2	44·5	44·3

It was found that fusion of potassium cryolite alone at temperatures above 900° leads to loss in weight, and also that sodium fluoride is volatile on heating.

(iv) *Sodium.* When it is desired to determine sodium content, it is necessary to decompose the cryolite with sulphuric acid, remove the aluminium, and use zinc uranyl acetate as precipitant.

The authors wish to thank the Chief Scientific Officer, Ministry of Supply, for permission to publish this paper.

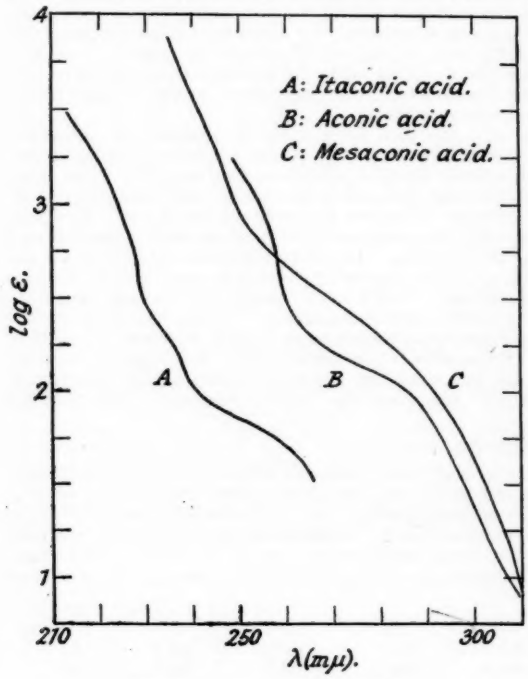
ARMAMENT RESEARCH DEPARTMENT, MINISTRY OF SUPPLY. [*Received, November 26th,* 1946.]

220. *Unsaturated Lactones. Some Esters of Aconic and Coumalic Acids.*

By N. R. Campbell and J. H. Hunt.

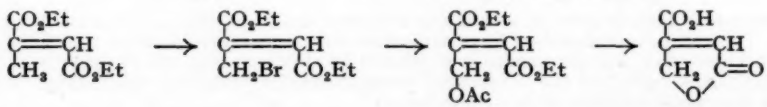
Aconic acid has been synthesised by a new method, which affords positive evidence for its acceptance as a β-substituted αβ-butenolide. The older method of preparation has been developed, and a series of esters of aconic and coumalic acids prepared. The results of simple toxicity tests on the acids and their esters are given.

Among the simpler unsaturated lactones examined by Chen, Elderfield, Steldt, and Fried (*J. Pharmacol.*, 1942, **74**, 381) for cardioactivity, the methyl and ethyl esters of coumalic acid were noteworthy for some positive result. It was considered desirable to extend this series of esters and to compare them biologically with a similar, related, series of esters of aconic acid.



The structure of coumalic acid is well established and probably beyond doubt, but there has been no positive evidence in support of the normally accepted βγ-position of the double bond in aconic acid. The structure of this acid was given by Fittig and Beer (*Annalen*, 1883, **216**, 92) as β-carboxybutenolide, but they were unable to allocate an exact position to the double bond. We have now prepared the αβ-acid by a method which does not involve conditions likely to cause migration, and have identified it with aconic acid prepared by the usual method from itaconic acid.

This new method of preparation involved bromination of the methyl group of diethyl mesaconate (diethyl methylfumarate) by means of *N*-bromosuccinimide, replacement of the bromine by an acetoxy-group under mild conditions, hydrolysis with barium hydroxide, and cyclisation by warming with water.



This evidence of structure brings aconic acid into line with the series of substituted butenolides which includes the aglycones of the digitalis and strophanthus groups of heart-poisons. The latter were also considered to be βγ-butenolides before the work of Elderfield, Paist, Blout, and Uhle (*J. Org. Chem.*, 1941, **6**, 273) who produced evidence suggesting the present accepted αβ-structure.

We have examined the ultra-violet absorption of aconic acid and compared the results with those obtained by Bielecki and Henri (*Ber.*, 1913, **46**, 2602) on mesaconic and itaconic acids, which are open-chain analogues of the two possible structures for aconic acid; we find that the absorption of aconic acid corresponds more closely to that of the fully conjugated isomer, thereby supplying further evidence for the αβ-disposition of the double bond in aconic acid (see Fig.).

The preparation of aconic acid from itaconic acid was also studied. Itaconic acid was prepared by pyrolysis of citric acid (*Org. Synth.*, 1943, Coll. Vol. 2, 368); the isolation of acetone as a by-product together with approximately the theoretical volume of carbon monoxide indicated that acetonedicarboxylic acid was among the primary products of pyrolysis. Itaconic acid was brominated and the resulting " itadibromopyro-tartaric acid " (not isolated) converted into sodium aconate by a modification of the method used by Meilly (*Annalen*, 1874, **171**, 153), giving a greatly improved yield.

Esters of coumalic acid have been prepared by von Pechmann (*Annalen*, 1891, **264**, 279), Ruzicka (*Helv. Chim. Acta*, 1921, **4**, 504), and Caldwell, Tyson, and Lauer (*J. Amer. Chem. Soc.*, 1944, **66**, 1483). The method employed has generally involved treatment of a sulphuric acid solution of coumalic acid with the required alcohol, the coumalic acid being frequently prepared *in situ* from malic acid. We have employed both versions of this method and have also used much smaller (catalytic) quantities of sulphuric acid with azeotropic removal of water. Replacement of sulphuric acid by hydrogen chloride was not successful. We have compared the yields of one ester by the four methods; the first gave a considerably higher yield than the others.

The methyl and ethyl esters of aconic acid have been described by Meilly (*loc. cit.*), Reiter and Bender (*Annalen*, 1905, **339**, 316), and Wislicenus, Böklen, and Reuthe (*ibid.*, 1908, **363**, 353). The most suitable method for preparation of aconic esters is by reaction of silver aconate with the appropriate alkyl halide, usually at elevated temperature. With the exception of the *n*-butyl ester, the aconates prepared have all been obtained as crystalline solids; the *iso*propyl ester has been obtained in liquid and solid forms, both with satisfactory analyses. Ethyl aconate was described by Wislicenus (*loc. cit.*) as a liquid; under identical conditions we obtained a crystalline product.

While Rast's method gave satisfactory results for the molecular weights of all coumalates prepared, the aconates showed values ranging from theoretical to three times theoretical. We have been unable to explain this, or to correlate these anomalous results with the existence of solid and liquid forms.

Biological Investigation.—As a result of solubility difficulties in testing of these and other compounds by the usual assay method for digitalis, we adopted a simple toxicity test, the assumption being made that high cardioactivity might be accompanied by high toxicity. The substances were dissolved or suspended in arachis oil and administered subcutaneously to mice; median lethal doses (L.D./50) were calculated from the number of deaths after four days.

Toxicities in the coumalate series appear to decrease with increasing length of the alkyl chain, rather than with increasing molecular weight; the level of toxicity in the aconate series was so low that massive doses would be required for any variations to become apparent. It seems improbable that notable toxicity or cardioactivity will be found among simple esters of either of these acids.

	L.D./50.		L.D./50.
Coumalic acid	0·8 mg./g.	n-*Butyl coumalate*	>1 mg./g.
Methyl coumalate	0·3 mg./g.	iso*Butyl coumalate*	0·6 mg./g.
Ethyl coumalate	0·33 mg.g/.	*Benzyl coumalate*	>1 mg./g.
n-*Propyl coumalate*	0·55 mg./g.	cyclo*Hexyl coumalate*	0·55 mg./g.
iso*Propyl coumalate*	0·4 mg./g.		

Aconic acid, methyl aconate, ethyl aconate, n-*propyl aconate*, iso*propyl aconate*, n-*butyl aconate*, iso*butyl aconate*, *benzyl aconate*, and cyclo*hexyl aconate*, all showed L.D./50 >1 mg./g.

Experimental.

Sodium Aconate.—Itaconic acid (260 g.) was stirred to a paste with water (340 c.c.), and bromine (320 g.) slowly added, the temperature not being allowed to rise above 50°. When all but a trace of bromine had disappeared, the solution was neutralised with sodium hydrogen carbonate (336 g.). The mixture was then heated to 50° on the water-bath and treated with a suspension of sodium carbonate (106 g., anhydrous) in water (158 c.c.) at 50°, added in small portions until the solution remained neutral to bromothymol-blue. The mixture was cooled and allowed to remain at 0° for 1 hour. The crystalline sodium salt was filtered off, washed with iced water and with 95% alcohol, and dried in a vacuum at 110°. Yield of anhydrous sodium aconate, 179 g. (59%).

Silver Aconate.—Sodium aconate (100 g.) was stirred with water (80 c.c.) and heated to 40°. Silver nitrate (112·5 g.) dissolved in warm water (40 c.c.) was added, the mixture cooled to 0°, and the crystalline precipitate filtered off, washed with iced water and methanol, and dried in a vacuum desiccator. Yield, 147 g. (94%).

Aconic Acid.—Anhydrous sodium aconate (10 g.) was suspended in dry ether (30 c.c.). Dry hydrogen chloride was then passed in with stirring, until a gain in weight of 3·0 g. was obtained. The mixture was left overnight, the solid (11·5 g.) filtered off and extracted with ether in a continuous extractor. Removal of solvent left 7·6 g. of aconic acid, m.p. 162°. A further 0·7 g. of impure aconic acid, m. p. 156°, was obtained by evaporation of the original mother liquor. Total yield. 97%.

Ethyl Aconate (cf. Wislicenus, *loc. cit.*).—Silver aconate (30 g.) and ethyl iodide (15 c.c.) were heated in a sealed tube at 100° for 4 hours. The contents of the tube were extracted with ether, the extract washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$), and the solvent removed. The residue (15·5 g.) was distilled at reduced pressure, 8·95 g. of partly crystalline material (b. p. 132°/15 mm.) being collected. The crystals were separated and recrystallised from methanol at − 10°. Yield, 3·3 g.; m. p. 64° (Found: C, 53·87; H, 5·31; *M*, 478. Calc. for $C_7H_8O_4$: C, 53·51; H, 5·13%; *M*, 157).

n-*Propyl Aconate.*—Silver aconate (20 g.) was refluxed for 1½ hours with *n*-propyl bromide (20 c.c.), excess of bromide then distilled off, and the residue diluted with ether and filtered. The brown oil (10·1 g.) remaining after removal of the ether was distilled, yielding 4·4 g. of partly crystalline material (b. p. 80—88°/0·1 mm.) which was dried on a porous tile. The *ester*, recrystallised from benzene–*cyclo*hexane, had m. p. 34° (Found: C, 56·2; H, 6·04; *M*, 286. $C_9H_{10}O_4$ requires C, 56·5; H, 5·92%; *M*, 170).

iso*Propyl Aconate.*—(*a*) Silver aconate (14 g.) and *iso*propyl bromide (10 c.c.) were heated in a sealed tube at 100° for 3 hours. The contents of the tube were extracted with ether and the ether and excess of *iso*propyl bromide removed by distillation, leaving a brown oil (5 g.). Distillation of this yielded the *ester* as a colourless oil (1·7 g.), b. p. 70—71°/0·1 mm., $n_D^{20°}$ 1·460 (Found: C, 56·4; H, 5·58; *M*, 213. $C_9H_{10}O_4$ requires C, 56·5; H, 5·92%; *M*, 170).

(*b*) *iso*Propyl iodide (14 c.c.) was added slowly to silver aconate (28 g.) and benzene (30 c.c.). On gently heating the mixture a violent reaction commenced, necessitating cooling. The mixture was then refluxed for 1½ hours and cooled. The insoluble material was filtered off, washed with benzene, and extracted with ether in a continuous extractor. The ethereal extract yielded aconic acid (4·0 g.). The benzene solution was washed with sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$). Removal of the benzene gave a brown oil (9·48 g.), which on distillation gave two fractions: (i) b. p. 88—92°/0·2 mm., (ii) b. p. 100—120°/0·1 mm. Fraction (ii) which was partly crystalline was dried on a porous tile and recrystallised from light petroleum (b. p. 40—60°); m. p. 80° (Found: C, 56·3; H, 5·81%; *M*, 172).

n-*Butyl Aconate.*—Silver aconate (12·7 g.) was heated with *n*-butyl iodide (8 c.c.) and benzene (20 c.c.) in a sealed tube at 100° for 1 hour. The product, treated as for *n*-propyl aconate, yielded the *ester* as a colourless oil (2·5 g.), b. p. 91°/0·1 mm., $n_D^{20°}$ 1·471 (Found: C, 58·8; H, 6·66; *M*, 491. $C_9H_{12}O_4$ requires C, 58·7; H, 6·57%; *M*, 184).

iso*Butyl Aconate.*—Silver aconate (25·4 g.) was refluxed for 1½ hours with *iso*butyl bromide (14 c.c.) and benzene (30 c.c.). The mixture was diluted with ether, filtered, and the filtrate washed with sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$). After removal of the ether the crude oily product (9·8 g.) was distilled under reduced pressure. The fraction, b. p. 86—88°/0·1 mm., partly crystallised and was dried on a porous plate. The solid *ester* was recrystallised from light petroleum (b. p. 60—80°); m. p. 114° (Found: C, 58·7; H, 6·58; *M*, 200. $C_9H_{12}O_4$ requires C, 58·7; H, 6·57%; *M*, 184).

Benzyl Aconate.—Silver aconate (11·5 g.) was refluxed for 1 hour with benzene (20 c.c.) and benzyl chloride (8·4 c.c.). The filtered benzene solution was washed with sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$). After removal of the benzene the *ester* was distilled under reduced pressure, b. p. 140°/0·04 mm., and recrystallised from *cyclo*hexane. Yield, 1·1 g.; m. p. 59—60° (Found: C, 66·03; H, 4·55; *M*, 384. $C_{12}H_{10}O_4$ requires C, 66·04; H, 4·62%; *M*, 218).

cyclo*Hexyl Aconate.*—Aconic acid (6·25 g.) was dissolved in cold concentrated sulphuric acid (10 c.c.), the solution cooled to 0°, and *cyclo*hexanol (15·8 c.c.) added. The mixture was allowed to warm to 18°, left for 20 hours, then poured on crushed ice and extracted with ether. After being washed, dried, and freed from solvent, the *ester* was crystallised from pentane (3·4 g.) and recrystallised from light petroleum (b. p. 60—80°); m. p. 68° (Found: C, 62·88; H, 6·72; *M*, 295. $C_{11}H_{14}O_4$ requires C, 62·84; H, 6·71%; *M*, 210).

iso*Propyl Coumalate.*—Malic acid (50 g.) was added slowly with stirring to fuming sulphuric acid (150 g.) containing 10% of sulphur trioxide, and the mixture heated on the water-bath until evolution of gas ceased. The mixture was then cooled and *iso*propyl alcohol (165 c.c.) added. After being heated on the water-bath for 1 hour under reflux, the mixture was cooled, poured on ice (200 g.), partly neutralised with sodium carbonate, left overnight, and filtered. The filtrate was extracted with ether, and the extract washed, dried and freed from solvent. The residual oil was distilled under reduced pressure. The fraction, b. p. 102—110°/0·1 mm., deposited crystals of the *ester* which were twice crystallised from light petroleum (b. p. 40—60°). Yield, 6 g.; m. p. 44° (Found: C, 59·4; H, 5·35; *M*, 171. $C_9H_{10}O_4$ requires C, 59·3; H, 5·41%; *M*, 182).

n-*Butyl Coumalate.*—Malic acid (100 g.), fuming sulphuric acid (300 g.), and *n*-butyl alcohol (200 c.c.) were brought into reaction by the method employed for *iso*propyl coumalate. After distillation of the crude reaction mixture, the fraction, b. p. 120—124°/0·1 mm., solidified on standing. The *ester* was twice recrystallised from light petroleum (b. p. 40—60°). Yield, 10 g.; m. p. 41° (Found: C, 61·4; H, 6·14; *M*, 191. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·16%; *M*, 196).

n-*Propyl Coumalate.*—(*a*) Malic acid (100 g.), fuming sulphuric acid (300 g.), and *n*-propyl alcohol (176 g.) were brought into reaction by the method employed for *iso*propyl coumalate. Yield of pure ester, 14 g. (20%).

(*b*) Coumalic acid (6·8 g.) was dissolved in concentrated sulphuric acid (13 g.) and cooled to room temperature. *n*-Propyl alcohol (13 g.) was added, and the mixture heated with occasional shaking, on the water-bath, under reflux for 1 hour and poured into iced water (50 c.c.). The solid was filtered off, washed, and dried (6 g.). The filtrate was extracted with ether and a further quantity of solid obtained, which was added to that previously obtained and distilled under reduced pressure. The fraction, b. p. 96—100°/0·1 mm., was crystallised from light petroleum (b. p. 60—80°). Yield of *ester*, 5 g. (57%); m. p. 59—60° (Found: C, 59·8; H, 5·74; *M*, 188. $C_9H_{10}O_4$ requires C, 59·3; H, 5·41%; *M*, 182).

(*c*) Coumalic acid (6·8 g.) was covered with *n*-propyl alcohol (13 g.) and saturated with dry hydrogen chloride at 0°. The mixture was allowed to warm to room temperature, and next day was poured into water. No ester could be isolated; unchanged coumalic acid (5 g.) was recovered.

(*d*) A mixture of coumalic acid (6·8 g.), *n*-propyl alcohol (10·6 c.c.), toluene (10 c.c.), and concentrated sulphuric acid (2 drops) was distilled slowly, the distillate being dried (K_2CO_3) and returned. After 3 hours toluene and excess of propyl alcohol were distilled off. Yield of ester, 3 g. (34%).

iso*Butyl Coumalate.*—Coumalic acid (7·1 g.), concentrated sulphuric acid (15 g.), and *iso*butyl alcohol (17·5 c.c.) were brought into reaction by the method employed for *n*-propyl coumalate. The crude *ester*

was distilled and the fraction, b. p. 120—126°/0·1 mm., twice crystallised from light petroleum (b. p. 40—60°). Yield, 6 g.; m. p. 62° (Found: C, 61·1; H, 6·21; *M*, 199. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·12%; *M*, 196).

Benzyl Coumalate.—Silver coumalate (4·5 g.) (von Pechmann, *loc. cit.*) was refluxed for 1 hour with benzyl chloride (5 c.c.) and benzene (15 c.c.). The filtered benzene solution was washed and dried. Removal of the benzene left an oil (2·7 g.), which was distilled under reduced pressure, b. p. 140—150°/0·05 mm., and crystallised twice from ether. Yield of *ester*, 0·52 g.; m. p. 92° (Found: C, 67·9; H, 4·19; *M*, 238. $C_{13}H_{11}O_4$ requires C, 67·8; H, 4·35%; *M*, 230).

cyclo*Hexyl Coumalate.*—Coumalic acid (12·6 g.) was dissolved in concentrated sulphuric acid (25 c.c.) and the mixture cooled to 0°. *cyclo*Hexanol (45 c.c.) was added and the mixture allowed to warm to room temperature and left for 3 days. The mixture was worked up as under *cyclo*hexyl aconate, yielding 6·5 g. of crude crystalline *ester* which after further crystallisation (charcoal) from light petroleum (b. p. 60—80°) had m. p. 70° (Found: C, 65·09; H, 6·46; *M*, 224. $C_{12}H_{14}O_4$ requires C, 64·8; H, 6·35%; *M*, 222).

Diethyl γ-Bromomesaconate.—(*a*) Diethyl mesaconate (71 g.) was refluxed with *N*-bromosuccinimide (71 g.) and carbon tetrachloride (213 c.c.) for 30 hours. The mixture was cooled, filtered, freed from solvent, and diluted with light petroleum (b. p. 40—60°) (200 c.c.) which precipitated traces of succinimide. After filtration and removal of solvent the *ester* was distilled, b. p. 91°/0·1 mm. Yield, 52 g. (Found: C, 39·8; H, 5·07; Br, 33·6. $C_9H_{13}O_4Br$ requires C, 40·77; H, 4·94; Br, 30·14%).

(*b*) Diethyl mesaconate (48·5 g.) was heated under reflux with *N*-bromosuccinimide (31 g.), carbon tetrachloride (50 c.c.), and benzoyl peroxide (2·4 g.) for 1 hour. The mixture was filtered and the filtrate washed and dried. After removal of solvent the residue (60·0 g.) was distilled; unchanged diethyl mesaconate (18·2 g., b. p. 60—65°/0·15 mm.) was followed by the main fraction, b. p. 94—98°/0·15 mm. (31·3 g.), which was redistilled; b. p. 72°/0·10 mm., $n_D^{20°}$ 1·485 (Found: C, 40·71; H, 5·04; Br, 31·3%). Repeated distillation of the ester failed to give a product with a correct bromine analysis.

Aconic Acid.—Diethyl γ-bromomesaconate (10 g.) was heated for 1 hour on the water-bath, under reflux, with potassium acetate (5 g. fused) in absolute alcohol (50 c.c.). The mixture was cooled and filtered, most of the alcohol distilled off, and the residue taken up in benzene. The resulting oil was distilled, 7·23 g. being collected, b. p. 96°/0·1 mm.

The crude acetoxy-derivative (4·2 g.) was stirred for 1½ hours at room temperature with water (50 c.c.), and barium hydroxide (8·15 g.) was gradually added. The slightly cloudy solution was filtered and treated with 5N-sulphuric acid (10·5 c.c.). After removal of the barium sulphate, the solution was heated at 70° for ½ hour and then gave a deep purple colour in the Legal test whereas no colour was produced before heating. Extraction with ether in a continuous extractor gave a mass of sticky crystals which were washed with a little dry ether. Yield, 0·6 g. of crystals, m. p. 164°, which did not depress the m. p. of aconic acid (Found: C, 46·84; H, 3·31. Calc. for $C_5H_4O_4$: C, 46·89; H, 3·14%). The methyl ester (from the silver salt and methyl iodide) had m. p. 82° and did not depress the m. p. of methyl aconate.

Our thanks are due to Prof. Buttle and to Dr. M. Vogt, both of the Pharmacology Dept., the College of the Pharmaceutical Society, for their co-operation in working out details of the toxicity test employed and for preliminary tests (not quoted here). All the biological results were determined by Dr. H. O. J. Collier of the Pharmacology Dept. of this Company, to whom our thanks are also due. Ultra-violet absorption determinations were kindly carried out by Mr. H. F. W. Kirkpatrick. We desire also to thank the Directors of Messrs. Allen & Hanburys Ltd. for permission to publish.

ALLEN & HANBURYS LTD., WARE. [*Received, November 27th,* 1946.]

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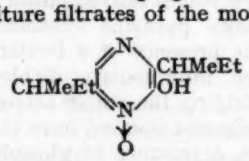
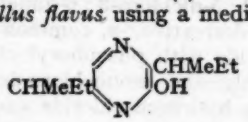
221. *Pyrazine Derivatives. Part III. Conversion of Diketopiperazines into Pyrazine Derivatives. Synthesis of* 2-*Hydroxy*-3 : 6-*di*-sec.-*butylpyrazine from* iso*Leucine.*

By R. A. BAXTER and F. S. SPRING.

A method for the conversion of diketopiperazines (α-amino-acid anhydrides) into pyrazine derivatives is described. *iso*Leucine anhydride (IX) has been converted into 2-chloro-3 : 6-di-*sec.*-butylpyrazine (XI) and thence into 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (II), and similarly alanine anhydride (III) has been converted into 2-chloro- (IV) and 2-hydroxy-3 : 6-dimethylpyrazine (VII).

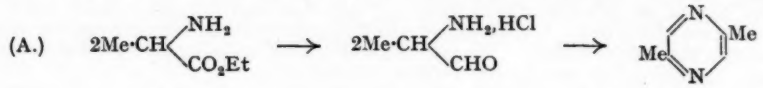
THE antibacterial substance aspergillic acid, for which the structure (I) has been suggested, is obtained from culture filtrates of the mould *Aspergillus flavus* using a medium containing an

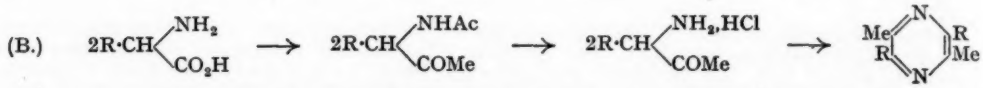
(I.)  (II.) 

amino-acid source such as tryptone. The present paper describes some preliminary experiments undertaken with the object of developing a synthetic route, starting from *iso*leucine, to

aspergillic acid or to the related deoxyaspergillic acid for which structure (II) has been suggested (for literature see Newbold and Spring, this vol., p. 373).

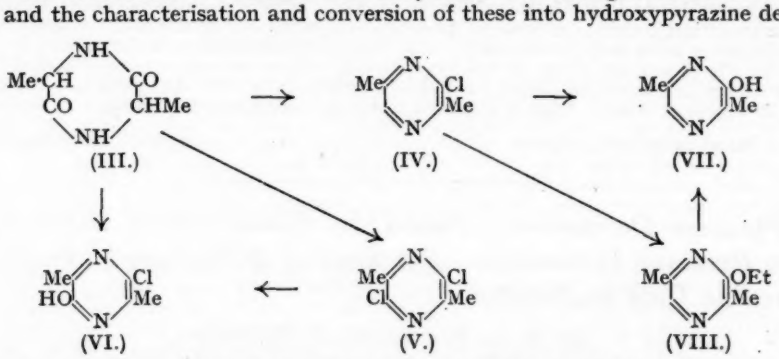
Two syntheses of pyrazine bases from α-amino-acids have been described. Reduction of the ethyl ester of alanine with sodium amalgam in the presence of hydrochloric acid gave the hydrochloride of α-aminopropaldehyde which when treated with alkali and mercuric chloride yielded 2 : 5-dimethylpyrazine in poor yield (A) (Neuberg, *Ber.*, 1908, **41**, 956; Fischer, *ibid.*, p.





1019). The second synthesis (B) consists in treatment of an α-amino-acid with acetic anhydride and pyridine to yield an α-acetamido-ketone which, when hydrolysed with hydrochloric acid, gave the corresponding α-amino-ketone hydrochloride. The latter when condensed with alkali in the presence of an oxidising agent gave a fully substituted pyrazine base (Dakin and West, *J. Biol. Chem.*, 1928, **78**, 745, 757).

Our method of approach to the problem consisted in a study of methods for converting a diketopiperazine (α-amino-acid anhydride) into an aromatic pyrazine derivative. The simplest reaction of this type would involve oxidation of a diketopiperazine to a dihydroxypyrazine, but so far as we are aware no transformation of this type has been reported. Abderhalden (*Z. physiol. Chem.*, 1924, **140**, 52; 1925, **143**, 128; 1925, **144**, 234) has shown that oxidation of glycine anhydride with potassium permanganate or with hydrogen peroxide and ferrous sulphate yields oxamide (cf. Ludtke, *Biochem. Z.*, 1925, **143**, 158), and according to Arai (*ibid.*, 1930, **226**, 233) glycine anhydride and phenylalanine anhydride on prolonged shaking with oxygen both yield urea. Goldschmidt and Steigenwald (*Ber.*, 1925, **58**, 1346) have shown that treatment of alanine anhydride with hypobromite yields an imidazolone derivative (cf. Goldschmidt, Wiberg, Nagel, and Martin, *Annalen*, 1927, **456**, 1). The present paper describes a method for the conversion of α-amino-acid anhydrides into halogen substituted pyrazine derivatives and the characterisation and conversion of these into hydroxypyrazine derivatives.



Treatment of *dl*-alanine anhydride (III) with phosphoryl chloride gives a mixture of **2-*chloro*-3 : 6-*dimethylpyrazine*** (IV) and **2 : 5-*dichloro*-3 : 6-*dimethylpyrazine*** (V). Separation of the two reaction products is relatively simple since the dichloro-derivative is not basic, whereas 2-chloro-3 : 6-dimethylpyrazine is soluble in 3N-hydrochloric acid. The formation of the monochloro-derivative (IV) from alanine anhydride does not involve an oxidation step, whereas the formation of 2 : 5-dichloro-3 : 6-dimethylpyrazine involves the oxidation of an intermediate dihydropyrazine derivative, a common step in many pyrazine syntheses. Treatment of *dl*-alanine anhydride with phosphoryl chloride in the presence of a tertiary base (dimethylaniline) gives only the monochloro-derivative, the intermediate dichlorodihydropyrazine presumably losing hydrogen chloride and thereby yielding the stable aromatic 2-chloro-3 : 6-dimethylpyrazine. 2-Chloro-3 : 6-dimethylpyrazine was not isolated from the reaction product obtained by treatment of *dl*-alanine anhydride with a mixture of phosphoryl chloride and phosphorus pentachloride (as oxidising agent), the reaction giving 2 : 5-dichloro-3 : 6-dimethylpyrazine in poor yield, together with a small quantity of **2-*chloro*-5-*hydroxy*-3 : 6-*dimethylpyrazine***

(VI); the latter was the only isolated product of the reaction between *dl*-alanine anhydride and phosphorus pentachloride.

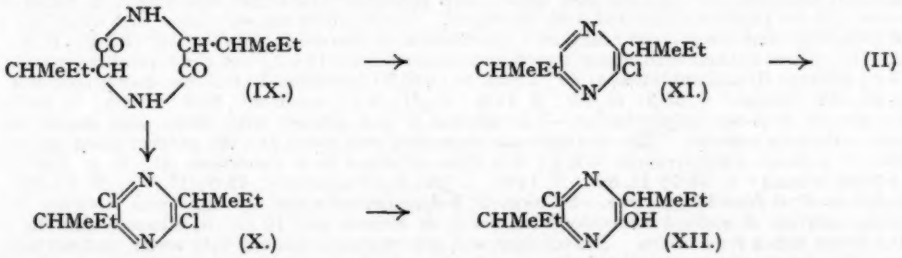
Prolonged treatment of 2-chloro-3 : 6-dimethylpyrazine with concentrated potassium hydroxide solution gives 2-hydroxy-3 : 6-dimethylpyrazine (VII) identical with that previously obtained by different synthetic methods (Baxter, Newbold, and Spring, this vol., p. 370). Less drastic methods for the replacement of the halogen atom by hydroxyl were sought, but so far we have not succeeded in replacing the halogen by an amino-group. Treatment of 2-chloro-3 : 6-dimethylpyrazine with alcoholic sodium ethoxide yields 2-*ethoxy*-3 : 6-*dimethylpyrazine* (VIII), hydrolysis of which with hydrochloric acid gives 2-hydroxy-3 : 6-dimethylpyrazine (VII).

Treatment of 2 : 5-dichloro-3 : 6-dimethylpyrazine with concentrated aqueous alkali yields 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine (VI). This compound is soluble in alkali and reprecipitated from alkaline solution on acidification: its ultra-violet absorption spectrum is very similar to those of the simple hydroxypyrazine derivatives examined by Newbold and Spring (this vol., p. 373). 2-Chloro-5-hydroxy-3 : 6-dimethylpyrazine was recovered unchanged after treatment under drastic conditions with alcoholic ammonia. Although attempts to convert it into 2-hydroxy-3 : 6-dimethylpyrazine by reduction in alkaline solution with Raney alloy [Schwenk and Papa, *J. Org. Chem.*, 1944, **9**, 1; *Ind. Eng. Chem.* (*Anal.*), 1943, **15**, 576] were unsuccessful, this transformation was effected by heating 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine with solid potassium hydroxide. Treatment of 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine with phosphoryl chloride using conditions which successfully convert *dl*-alanine anhydride into a mixture of 2-chloro- and 2 : 5-dichloro-3 : 6-dimethylpyrazine gives a very small yield of 2 : 5-dichloro-3 : 6-dimethylpyrazine, the starting material being largely recovered unchanged.

The reaction stages described above constitute a conversion of *dl*-alanine into 2-hydroxy-3 : 6-dimethylpyrazine. It was of great interest, therefore, to attempt to convert *dl-iso*leucine into 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine in order to compare the product with the racemate previously obtained by Newbold and Spring (*loc. cit.*) by a different synthetic route.

Ehrlich (*Ber.*, 1907, **40**, 2550) obtained an *iso*leucine anhydride by heating *d-iso*leucine and commented that the compound was probably a mixture of isomers. Dutcher and Wintersteiner (*J. Biol. Chem.*, 1944, **155**, 359) describe a racemic *iso*leucine anhydride prepared from *dl-iso*leucine. Using a modification of the method developed by Sannié (*Bull. Soc. chim.*, 1942, **9**, 487) for the preparation of amino-acid anhydrides in which the α-amino-acid is heated with ethylene glycol, *dl-iso*leucine gave a *dl-iso*leucine anhydride in 49% yield. In a second method, α-bromo-β-methylvaleryl chloride was reacted with *dl-iso*leucine methyl ester hydrochloride and the product heated with alcoholic ammonia to yield a *dl-iso*leucine anhydride. Although the specimens of anhydride obtained by the two methods appear to be identical, it is clear that they may comprise different mixtures of isomers.

Treatment of *dl-iso*leucine anhydride (IX) with phosphoryl chloride gives a mixture of 2 : 5-*dichloro*-3 : 6-*di*-sec.-*butylpyrazine* (X) and 2-*chloro*-3 : 6-*di*-sec.-*butylpyrazine* (XI). The halogen substituents in these pyrazine derivatives are even less reactive than those in the corresponding dimethyl homologues. Thus 2-chloro-3 : 6-di-*sec.*-butylpyrazine was recovered unchanged after prolonged refluxing with 20% potassium hydroxide solution, conditions which



converted 2-chloro-3 : 6-dimethylpyrazine into 2-hydroxy-3 : 6-dimethylpyrazine. When heated to 180° with powdered potassium hydroxide, however, 2-chloro-3 : 6-di-*sec.*-butylpyrazine yielded 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (II) identical with the racemate obtained previously from di-*sec.*-butylpyrazine. 2 : 5-Dichloro-3 : 6-di-*sec.*-butylpyrazine was also unchanged after treatment with concentrated aqueous alkali, but when heated with powdered potassium hydroxide it gave 2-*chloro*-5-*hydroxy*-3 : 6-*di*-sec.-*butylpyrazine* (XII).

Experimental.

2 : 5-*Dichloro*-3 : 6-*dimethylpyrazine*.—A mixture of 2 : 5-diketo-3 : 6-dimethylpiperazine prepared from *dl*-alanine by the method described by Sannié (*loc. cit.*) (5 g.) and phosphoryl chloride (50 c.c.) was heated at 120° (bath temp.) for 20 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue triturated with ice–water. The solid was collected (filtrate *A*), washed with water, and dried over phosphoric oxide (yield, 1·3 g.). Sublimation of this material at 60—80°/2 mm. gave 2 : 5-*dichloro*-3 : 6-*dimethylpyrazine* as prisms, m. p. 73° (Found: C, 41·1; H, 3·7; N, 15·4. $C_6H_6N_2Cl_2$ requires C, 40·7; H, 3·4; N, 15·8%). Light absorption in alcohol: Maximum at 2975 A., $\epsilon = 810$.

2-*Chloro*-3 : 6-*dimethylpyrazine*.—The filtrate *A* was treated with sodium carbonate solution until just alkaline and the mixture extracted with ether. The extract was dried, the ether removed, and the residue distilled to yield 2-*chloro*-3 : 6-*dimethylpyrazine* as an oil, b. p. 78°/15 mm. (1·4 g.), $n_D^{19°}$ 1·5284 (Found: C, 50·2; H, 4·8. $C_6H_7N_2Cl$ requires C, 50·5; H, 4·9%). 2-Chloro-3 : 6-dimethylpyrazine is soluble in 3N-hydrochloric acid. It forms a picrate, m. p. approx. 100°, and a chloroplatinate, m. p. > 360°, which are extremely soluble in the common solvents; this extreme solubility precluded their satisfactory purification.

Treatment of alanine anhydride (5 g.) with phosphoryl chloride (30 c.c.) and dimethylaniline (10 c.c.) for 20 minutes at 120° gave 2-chloro-3 : 6-dimethylpyrazine (1 g.). Difficulty was experienced in separating the product from the dimethylaniline; this may account for the low yield.

2-*Chloro*-5-*hydroxy*-3 : 6-*dimethylpyrazine*.—(*a*) A mixture of *dl*-alanine anhydride (5 g.), phosphorus pentachloride (5 g.), and phosphoryl chloride (15 c.c.) was refluxed for 30 minutes. Excess of phosphoryl chloride was removed by distillation and the residue triturated with water to give 2 : 5-dichloro-3 : 6-dimethylpyrazine (0·5 g.), m. p. and mixed m. p. 72—73°. The mother liquor was neutralised with sodium carbonate and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extract gave a solid (0·8 g.) which, after crystallisation from benzene (needles) followed by sublimation, gave 2-*chloro*-5-*hydroxy*-3 : 6-*dimethylpyrazine* as needles, m. p. 224°. Although sparingly soluble in water, it is soluble in dilute sodium hydroxide and precipitated from this solution on acidification (Found: C, 45·6; H, 4·7. $C_6H_7ON_2Cl$ requires C, 45·4; H, 4·4%).

(*b*) A solution of 2 : 5-dichloro-3 : 6-dimethylpyrazine (0·5 g.) in dioxan (4 c.c.) and aqueous potassium hydroxide (10 c.c.; 20%) was refluxed for 20 hours. The solution was acidified with hydrochloric acid, the crystalline solid collected and purified by sublimation at 140°/1 mm. to give 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine (0·35 g.) as needles, m. p. 224°, either alone or when mixed with the specimen described above (Found: N, 17·5. $C_6H_7ON_2Cl$ requires N, 17·7%). Light absorption in alcohol: Maxima at 2285 A., $\epsilon = 10{,}000$ and 3330 A., $\epsilon = 6{,}800$.

dl-iso*Leucine Anhydride*.—(*a*) *dl-iso*Leucine (9 g.) was refluxed with ethylene glycol (54 c.c.) for 4 hours. The crude anhydride (2 g.) which separated on standing was purified by extraction with chloroform and evaporation of the chloroform filtrate. On crystallisation of the residue from alcohol, *dl-iso*leucine anhydride formed felted needles, m. p. 270° (sintering at 259°) (yield 49%) (Found: C, 63·5; H, 9·6. Calc. for $C_{12}H_{22}O_2N_2$: C, 63·7; H, 9·7%).

(*b*) An ice-cooled suspension of *dl-iso*leucine methyl ester hydrochloride (6·2 g.) in chloroform (80 c.c.) and α-bromo-β-methylvaleryl chloride (8 g.) was stirred and treated during 1 hour with a solution of *n*-butylpiperidine (22 g.) in chloroform (20 c.c.). The ice-bath was removed and the mixture stirred for a further hour. The chloroform solution was washed successively with water, dilute hydrochloric acid, sodium carbonate solution, and water. Evaporation of the dried chloroform solution under reduced pressure gave a semi-solid mass which did not crystallise completely. It was dissolved in ethanol (150 c.c.), the solution saturated with ammonia at 0° and heated at 180° for 8 hours. The reaction mixture was evaporated to dryness and the residue extracted with chloroform. The chloroform extract was evaporated and the product (1·4 g.) crystallised from alcohol to yield *dl-iso*leucine anhydride as needles, m. p. 270°, sintering at 260°. A mixture of this anhydride with a specimen prepared by method (*a*) softened at 260° and melted at 270° (Found: C, 64·2; H, 9·6; N, 12·6. Calc. for $C_{12}H_{22}O_2N_2$: C, 63·7; H, 9·7; N, 12·4%).

2 : 5-*Dichloro*-3 : 6-*di*-sec.-*butylpyrazine*.—*dl-iso*Leucine anhydride (2·0 g.) was refluxed with phosphoryl chloride (20 c.c.) for one hour. The phosphoryl chloride was removed under reduced pressure and the product triturated with ice–water. The mixture was extracted with ether, the extract dried (Na_2SO_4), and the solvent removed. Distillation of the residue gave an oil (1·2 g.), b. p. 118°/12 mm. The oil was shaken with concentrated hydrochloric acid (15 c.c.) and the crystalline mass collected (0·15 g.) (filtrate B) and sublimed at 50°/1 mm. to yield 2 : 5-*dichloro*-3 : 6-*di*-sec.-*butylpyrazine* as plates, m. p. 58—60° (Found: C, 55·3; H, 6·9; N, 10·9. $C_{12}H_{18}N_2Cl_2$ requires C, 55·2; H, 6·9; N, 10·7%).

2-*Chloro*-3 : 6-*di*-sec.-*butylpyrazine*.—The filtrate B was diluted with water and neutralised with sodium carbonate solution. The mixture was extracted with ether and the extract dried and distilled; 2-*chloro*-3 : 6-*di*-sec.-*butylpyrazine* (0·8 g.) was thus obtained as a colourless oil; b. p. 116°/12 mm., $n_D^{15°}$ 1·5030 (Found: C, 64·2; H, 8·5; N, 12·0. $C_{12}H_{19}N_2Cl$ requires C, 63·6; H, 8·4; N, 12·4%).

2-*Ethoxy*-3 : 6-*dimethylpyrazine*.—2-Chloro-3 : 6-dimethylpyrazine (1 g.) was treated with an alcoholic solution of sodium ethoxide (from 0·4 g. of sodium and 10 c.c. of ethanol) and the mixture heated under reflux for 4 hours. The solution was concentrated, diluted with water, and extracted with ether. The dried extract was distilled to give 2-*ethoxy*-3 : 6-*dimethylpyrazine* (0·7 g.) as a colourless oil, b. p. 81°/15 mm., $n_D^{15°}$ 1·4993 (Found: C, 62·8; H, 7·7; N, 18·5. $C_8H_{12}ON_2$ requires C, 63·2; H, 7·9; N, 18·4%). The *picrate* separated as prismatic needles from methanol, m. p. 108—109° (Found: C, 44·4; H, 4·2; N, 18·8. $C_{14}H_{15}O_8N_5$ requires C, 44·1; H, 3·9; N, 18·4%).

2-*Hydroxy*-3 : 6-*dimethylpyrazine*.—(*a*) 2-Chloro-3 : 6-dimethylpyrazine (1 g.) was heated under reflux with aqueous potassium hydroxide (20%; 10 c.c.) for 18 hours. The solution was neutralised (litmus) with hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with benzene and the extract concentrated; 2-hydroxy-3 : 6-dimethylpyrazine (0·6 g.) then

separated as needles. After recrystallisation from the same solvent it had m. p. 208—210° either alone or when mixed with an authentic specimen.

(*b*) A solution of 2-ethoxy-3 : 6-dimethylpyrazine (0·6 g.) in hydrochloric acid (5N, 20 c.c.) was heated under reflux for 18 hours. The solution was evaporated to dryness, the residue dissolved in water, and the solution neutralised by the addition of sodium carbonate solution and evaporated to dryness. The residue was extracted with benzene and the extract concentrated; 2-hydroxy-3 : 6-dimethylpyrazine (0·4 g.), m. p. and mixed m. p. 208—210°, then separated as needles.

(*c*) 2-Chloro-5-hydroxy-3 : 6-dimethylpyrazine (0·5 g.) was heated at 180—200° for 5 hours with powdered potassium hydroxide (2 g.). The cold reaction product was dissolved in water, and the solution neutralised with dilute hydrochloric acid and then evaporated to dryness (reduced pressure). Extraction with benzene in the usual manner gave 2-hydroxy-3 : 6-dimethylpyrazine (0·2 g.) as needles, m. p. and mixed m. p. 208—210°. The picrate separated as blades from methanol, m. p. 180—182°, undepressed when mixed with the specimen described by Baxter, Newbold, and Spring (*loc. cit.*).

2-*Hydroxy*-3 : 6-*di*-sec.-*butylpyrazine*.—2-Chloro-3 : 6-di-*sec.*-butylpyrazine (0·5 g.) was heated with powdered potassium hydroxide (2 g.) for 4 hours at 180°. The reaction mass was dissolved in water and the solution extracted with ether. The alkaline solution was acidified; 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (0·3 g.) then separated. It was collected and purified by sublimation at 110°/1 mm., and so obtained as small needles, m. p. 122—124°, not depressed when mixed with a specimen, m. p. 122—124°, prepared as described by Newbold and Spring (*loc. cit.*). Light absorption in alcohol: Maxima at 3250 A., ϵ = 10,000 and 2290 A., ϵ = 9,100.

2-*Chloro*-5-*hydroxy*-3 : 6-*di*-sec.-*butylpyrazine*.—2 : 5-Dichloro-3 : 6-di-*sec.*-butylpyrazine (0·3 g.) was heated with powdered potassium hydroxide (2 g.) for 4 hours at 160—180°. The mass was dissolved in water and unchanged dichloro-compound (0·2 g.) isolated by extraction with ether. Acidification of the solution with hydrochloric acid gave a solid which after sublimation at 90°/1 mm. gave 2-*chloro*-5-*hydroxy*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 105—106°. It is freely soluble in the common organic solvents, but insoluble in water (Found: C, 59·4; H, 8·0. $C_{12}H_{19}ON_2Cl$ requires C, 59·4; H, 7·8%).

We thank Mr. J. J. Gallagher for assistance in some of the experiments described. Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Grant.

THE ROYAL TECHNICAL COLLEGE, GLASGOW, C.1. [*Received, November 27th*, 1946.]

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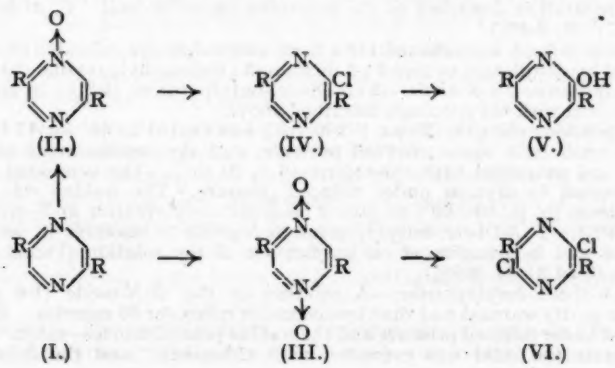
222. *Pyrazine Derivatives. Part IV. Pyrazine* N-*Oxides and their Conversion into Chloropyrazines.*

By G. T. NEWBOLD and F. S. SPRING.

2 : 5-Dialkylpyrazines are readily oxidised to a mixture of the corresponding mono- and di-*N*-oxides. The mono- and di-*N*-oxides are smoothly converted into 2-chloro- and 2 : 5-dichloro-3 : 6-dialkylpyrazines respectively. Hydrolysis of the 2-chloro-3 : 6-dialkylpyrazine gives the corresponding 2-hydroxy-3 : 6-dialkylpyrazine. By this route, 3 : 6-di-*sec.*-butylpyrazine yields a 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine identical with the racemate described by us in Parts II and III (this vol., p. 373, and preceding paper).

TREATMENT of 2 : 5-dimethylpyrazine (I, R = Me) with hydrogen peroxide in aqueous acetic acid gives 2 : 5-*dimethylpyrazine* N-*oxide* (II, R = Me) in 62% yield and 2 : 5-*dimethylpyrazine di*-N-*oxide* (III, R = Me) in 24% yield. Treatment of 2 : 5-dimethylpyrazine *N*-oxide with phosphoryl chloride gives 2-chloro-3 : 6-dimethylpyrazine (IV, R = Me) in 85% yield. Alkaline hydrolysis of the latter as described in the preceding paper yields 2-hydroxy-3 : 6-dimethylpyrazine (V, R = Me). This route to 2-hydroxy-3 : 6-dimethylpyrazine starting from 2 : 5-dimethylpyrazine is superior to that described by Baxter, Newbold, and Spring (this vol., p. 370).



2 : 5-Dimethylpyrazine di-*N*-oxide is converted by the action of phosphoryl chloride into 2 : 5-dichloro-3 : 6-dimethylpyrazine (VI, R = Me), identical with that described in the preceding paper. The yield, however, is low and is not increased by the use of sulphuryl chloride instead of phosphoryl chloride.

Treatment of 2 : 5-di-*sec.*-butylpyrazine (I, R = *sec.*-C_4H_9) with hydrogen peroxide gives a mixture of the corresponding mono- and di-*N*-oxides. 2 : 5-*Di*-sec.-*butylpyrazine di*-N-*oxide* (III, R = *sec.*-C_4H_9) is obtained in 64% yield, and on treatment with phosphoryl chloride it is converted into 2 : 5-dichloro-3 : 6-di-*sec.*-butylpyrazine (VI, R = *sec.*-C_4H_9), identical with that obtained from *iso*leucine anhydride. The mono-*N*-oxide (II, R = *sec.*-C_4H_9) was not isolated in a pure state; when treated with phosphoryl chloride it is converted into 2-chloro-3 : 6-di-*sec.*-butylpyrazine (IV, R = *sec.*-C_4H_9). The latter was characterised by hydrolysis to 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (V, R = *sec.*-C_4H_9), identical with the preparation described in the preceding paper and with that described in Part II (*loc. cit.*).

Experimental.

2 : 5-*Dimethylpyrazine Di*-N-*oxide*.—A solution of 2 : 5-dimethylpyrazine (5·5 g.) in glacial acetic acid (20 c.c.) was treated with hydrogen peroxide solution (40 c.c.; 100-vol.) and maintained at 56° for 16 hours. The solution was evaporated to small bulk under reduced pressure, and the residue was cooled in ice–water and made alkaline with sodium hydroxide solution. The mixture was extracted with chloroform (10 × 25 c.c.), the extract dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The solid residue was digested with boiling chloroform (25 c.c.), the mixture cooled, and the solid collected (filtrate *A*). Crystallisation from a large volume of chloroform gave 2 : 5-*dimethylpyrazine di*-N-*oxide* as needles (1·7 g.); it has no definite m. p., darkening profoundly at approximately 280°, and is not molten at 360°. The di-*N*-oxide is readily soluble in cold water but sparingly soluble in cold organic solvents. It is less soluble in 3N-sodium hydroxide solution than in water. It sublimes readily at 200°/0·5 mm. (Found: C, 51·3; H, 5·8. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7%).

2 : 5-*Dimethylpyrazine* N-*Oxide*.—The filtrate *A* and the mother liquors from the crystallisation of the di-*N*-oxide were combined, concentrated, and cooled, and some di-*N*-oxide was removed by filtration. The filtrate was evaporated to dryness and the solid residue (3·9 g.; m. p. 100°) was crystallised from benzene to give 2 : 5-*dimethylpyrazine* N-*oxide* as small colourless needles, m. p. 105—108°; it rapidly sublimes at 100°/0·001 mm. (Found: C, 58·0; H, 6·3. $C_6H_8ON_2$ requires C, 58·1; H, 6·45%). 2 : 5-Dimethylpyrazine *N*-oxide (0·6 g.) was heated with hydrogen peroxide solution (5 c.c.; 100-vol.) and glacial acetic acid (5 c.c.) for 18 hours at 56°. The reaction mixture was treated as described above to give 2 : 5-dimethylpyrazine di-*N*-oxide (0·5 g.), darkening at approximately 280° and not molten at 360° (Found: C, 51·5; H, 5·9%).

2-*Chloro*-3 : 6-*dimethylpyrazine*.—2 : 5-Dimethylpyrazine *N*-oxide (2·75 g.) was added in small portions to phosphoryl chloride (15 c.c.) with cooling and shaking. The mixture was cautiously warmed until solution was complete and the solution heated under reflux for 10 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured on crushed ice. The mixture was neutralised with sodium carbonate and extracted with chloroform (6 × 25 c.c.), and the combined extracts were dried ($NaSO_4$). The chloroform was evaporated and the residual oil distilled under reduced pressure to give a main fraction, b. p. 75—80°/12 mm. (2·7 g.; 85%), which on redistillation yielded 2-chloro-3 : 6-dimethylpyrazine as a colourless oil, b. p. 77°/12 mm.; $n_D^{19°}$ 1·5275 (Found: C, 50·8; H, 4·8; N, 19·4. Calc. for $C_6H_7N_2Cl$: C, 50·5; H, 4·9; N, 19·6%).

Hydrolysis of 2-chloro-3 : 6-dimethylpyrazine as described in the preceding paper gave a 50% yield of 2-hydroxy-3 : 6-dimethylpyrazine which after sublimation had m. p. 210—211°, undepressed on admixture with a specimen prepared *via* 2-amino-3 : 6-dimethylpyrazine (Baxter, Newbold, and Spring, *loc. cit.*).

2 : 5-*Dichloro*-3 : 6-*dimethylpyrazine*.—(*a*) 2 : 5-Dimethylpyrazine di-*N*-oxide (0·5 g.) was treated with phosphoryl chloride (2·5 c.c.) and heated under reflux for 30 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue triturated with ice–water. The solid was collected and purified by sublimation to yield 2 : 5-dichloro-3 : 6-dimethylpyrazine (100 mg.), m. p. 70—72°, not depressed by the preparation described in the preceding paper (Found: C, 41·0; H, 3·5. Calc. for $C_6H_6N_2Cl_2$: C, 40·7; H, 3·4%).

(*b*) The di-*N*-oxide (0·5 g.) was refluxed for 1 hour with sulphuryl chloride (10 c.c.). The excess of reagent was removed by distillation to give 2 : 5-dichloro-3 : 6-dimethylpyrazine (90 mg.), m. p. 71—73°, undepressed when mixed with the specimen described above.

2 : 5-*Di*-sec.-*butylpyrazine Di*-N-*oxide*.—2 : 5-Di-*sec.*-butylpyrazine (4·2 g.) in glacial acetic acid (30 c.c.) and hydrogen peroxide solution (30 c.c.; 100-vol.) was heated at 56° for 17 hours. The solution was evaporated to small bulk under reduced pressure, and the residue made alkaline with sodium hydroxide solution and extracted with chloroform (6 × 20 c.c.). The combined extracts were dried (K_2CO_3) and evaporated to dryness under reduced pressure. The residue was recrystallised from benzene–light petroleum (b. p. 40—60°) to give 2 : 5-*di*-sec.-*butylpyrazine di*-N-*oxide* as needles, m. p. 159—161° (yield 64%). 2 : 5-Di-*sec.*-butylpyrazine di-*N*-oxide is insoluble in water; it dissolves in 5N-hydrochloric acid and is precipitated on basification of the solution (Found: C, 64·2; H, 9·0. $C_{12}H_{20}O_2N_2$ requires C, 64·3; H, 8·9%).

2 : 5-*Dichloro*-3 : 6-*di*-sec.-*butylpyrazine*.—A mixture of the di-*N*-oxide (1·6 g.) and phosphoryl chloride (20 c.c.) was gently warmed and then heated under reflux for 30 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured into ice–water. After neutralisation with sodium carbonate the solid was extracted with chloroform, and the dried (Na_2SO_4) extract

evaporated to yield an oil which solidified on cooling. The solid was purified by sublimation at 50°/0·5 mm., and the sublimate crystallised from aqueous ethanol to yield 2 : 5-dichloro-3 : 6-di-*sec.*-butylpyrazine (46% yield) as laminæ, m. p. 59—61°, undepressed when mixed with the specimen described in the preceding paper (Found : C, 54·8; H, 6·9; N, 10·9. Calc. for $C_{12}H_{18}N_2Cl_2$: C, 55·2; H, 6·9; N, 10·7%).

2-*Chloro*-3 : 6-*di*-sec.-*butylpyrazine*.—The mother liquors from the crystallisation of 2 : 5-di-*sec.*-butylpyrazine di-*N*-oxide were evaporated. The viscous liquid (1·0 g.), which would not solidify, was heated under reflux with phosphoryl chloride (10 c.c.) for 30 minutes and the reaction mixture worked up in the usual manner to give 2-chloro-3 : 6-di-*sec.*-butylpyrazine (0·6 g.) as a colourless oil, b. p. 118—120°/14 mm.; $n_D^{20°}$ 1·5037 (Found : N, 12·1. Calc. for $C_{12}H_{19}N_2Cl$: N, 12·4%). Treatment of the chloro-compound (0·4 g.) with potassium hydroxide using the conditions described in the preceding paper gave 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (0·15 g.) as small needles which after sublimation had m. p. and mixed m. p. 121—123°.

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223. *Nitration in Sulphuric Acid. Part V. Nitration of 2 : 4-Dinitrotoluene in a Two-phase System.*

By G. M. BENNETT, J. C. D. BRAND, D. M. JAMES, T. G. SAUNDERS, and GWYN WILLIAMS.

The results of a series of experiments on the rate of nitration of dinitrotoluene in a two-phase system under various conditions are discussed in the light of the study of nitration in homogeneous sulphuric acid solution (Part IV, this vol. p. 474), but a complete analysis of the results is not possible owing to the lack of data concerning the concentrations in the two phases.

The rate of nitration for any one concentration of nitric acid is approximately proportional to the molar excess of sulphuric acid over water present.

Owing to the higher proportion of nitric acid and lower proportion of sulphuric acid present in comparison with the experiments in homogeneous solution, and also to solubility effects, there is no optimum composition of the acid mixture giving a maximum rate of nitration such as occurs with 92% sulphuric acid in homogeneous nitration. Consistently with this the influence of added bisulphates and nitrous acid is in all cases to depress the rate of reaction.

PART IV (*loc. cit.*) of this series described a study of the kinetics of nitration of 2 : 4-dinitrotoluene in homogeneous solution in sulphuric acid, with small concentrations of nitric acid and nitro-compound. The influence of water upon the rate of nitration was shown to be due to the production of bisulphate ion (equation 1), which exerts a dual influence, assisting nitration by increasing the proton-accepting quality of the medium and hindering nitration by its effect upon the extent to which nitric acid is converted into the nitronium ion NO_2^+ (equation 2). This ion is the effective nitrating agent (Part I, *J.*, 1946, 869).

$$H_2O + H_2SO_4 \longrightarrow OH_3^+ + HSO_4^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$HNO_3 + 2H_2SO_4 \rightleftharpoons NO_2^+ + OH_3^+ + 2HSO_4^- \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In actual practice, however, the conversion of dinitrotoluene (DNT) into trinitrotoluene (TNT), whether on the laboratory or on the industrial scale, is carried out with larger proportions of nitric acid and with sufficient organic material to produce a two-phase system. In this paper we present the results of laboratory experiments on the two-phase nitration of DNT, designed to show whether the influence of water upon the rate of nitration in a two-phase system is consistent with the conclusions derived from the experiments with homogeneous systems, and, in particular, to ascertain whether added bisulphate ion influences the rate of the two-phase nitration in a predictable manner. The results here described will be confined to those of importance for these two purposes : a more extensive account of the two-phase experiments, with full experimental details, will be published elsewhere.

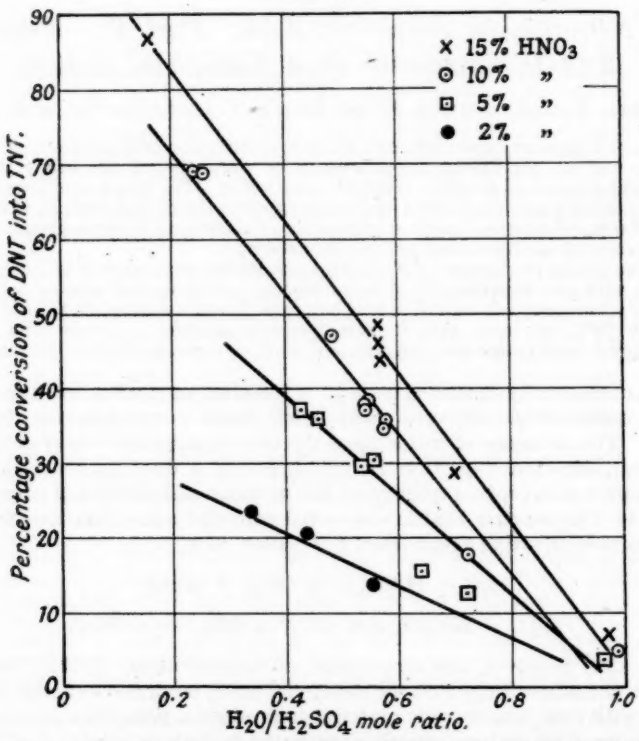
Method of Experiment.—In each nitration chosen quantities of reagents were vigorously stirred together at a specified temperature (usually 100°) for a certain time (usually 60 mins.), the reaction was stopped by pouring into water, and the composition of the organic products found, after washing and drying, by measurement of density with a pyknometer and by reference to a density–composition curve. The material subjected to nitration was usually a 50% dinitrotoluene–trinitrotoluene mixture in order to make the experiment similar in conditions to those found in one of the vessels of a nitrating plant where nitration is proceeding vigorously.

To determine strictly comparable rates of reaction would require the measurement of instantaneous initial velocities of the process, but the experimental errors would be large for

short times of reaction so that a compromise was necessary and the nitrations were continued for times sufficient to give changes large enough for accurate determination. A consideration of the various experimental errors shows that an observed change of 1% in the proportion of TNT present may be regarded as significant, but the corresponding calculated percentage conversion will be of the order of 2%.

Sulphuric Acid–Water Ratio.—The criteria we have used in examining the process are the H_2O/H_2SO_4 and the HNO_3/DNT molar ratios. Fig. 1 summarises the results obtained at 100° with widely varying H_2O/H_2SO_4 ratios for four different values of the HNO_3/DNT ratio, and shows clearly that nitration becomes negligible when the water/sulphuric acid ratio approaches unity. This is reminiscent of the nitration threshold found by Hetherington and Masson (*J.*, 1933, 105) for the nitration of nitrobenzene at 35°, but the latter substance has a much higher speed of nitration and, in presence of large amounts of nitric acid, its nitration continued to

FIG. 1.



Extent of nitration in 1 *hour at* 100° *of* 50% DNT *in* TNT *mixture with* 2·43 *wts. of mixed acids of various compositions.*

points somewhat beyond the 1 : 1 ratio of water to sulphuric acid. The results of our velocity measurements for the nitration of dinitrotoluene in homogeneous solution show values falling towards zero in the region of a H_2O/H_2SO_4 mole ratio of 0·87, and although this agrees approximately with the indications of Fig. 1 there appears to be a small but real discrepancy since appreciable nitration was found in two-phase experiments for acids of ratio 1·0. The explanation of this may lie in the slight change of composition of the acid mixture in consequence of the partition of water and acids between the two phases. Complete data on this point are not available, but some unpublished experiments by Mr. S. E. Napier, made to study the compositions of the two phases in such nitrations, showed that the aqueous acid present in the organic phase, amounting to 5—10% of that phase, always showed a H_2O/H_2SO_4 ratio much higher than that of the acid phase in equilibrium with it. This must result in the effective H_2O/H_2SO_4 molar ratio in two-phase nitrations being somewhat lower than that of the acid mixture as prepared and analysed before the experiment, and may well account for the discrepancy observed.

Fig. 1 shows that rates of nitration for each concentration of nitric acid fall in an approximately linear manner towards the point when $H_2O/H_2SO_4 = 1$, and this means that the rates are nearly proportional to $1 - H_2O/H_2SO_4$ or $(H_2SO_4 - H_2O)/H_2SO_4$, *i.e.*, nearly proportional to the fraction of sulphuric acid which is in molar excess of the water present. This is consistent with our view that nitration must depend on there being a molecular excess of sulphuric acid over the water present in the nitrating mixture, because the reaction (1) is complete, and it is only the excess of sulphuric acid which converts nitric acid into the active nitrating species NO_2^+ on which the reaction depends.

A detailed analysis of the results of these two-phase experiments in terms of the velocities of reaction determined in homogeneous sulphuric acid solution is, however, not at present possible because the available data as to the exact compositions of the two phases are far too fragmentary.

A remarkable regularity was observed in the course of some experiments carried out by Messrs. J. C. Dine and D. Fysh directed to answering the practical question " what is the necessary composition of mixed acid to give a specified extent of nitration? " It was found that for various concentrations of nitric acid (of 5% and upward when working at 100°) the required rate of nitration was obtained when the water mole-fraction had a certain value. Moreover, this was found to hold at three different temperatures, a necessary minimum concentration of nitric acid and a prescribed water mole-fraction being specified for each temperature.

A partial explanation of this result is again suggested by our theory when the concentrations of nitronium ion present in these acid mixtures are considered. Calculation from the ionic equilibria, using the constants determined in our study of kinetics in homogeneous sulphuric acid solution (Part IV, *loc. cit.*), shows that the acids giving the required rate of nitration have approximately constant concentrations of NO_2^+ ion. The data for six such acids found to give a prescribed rate of 16·5% conversion of DNT in 30 minutes at 100° are shown in the table

Composition of nitrating acids giving a specified rate of nitration at 100°.

	Wt., %.			Mole-fractions.			
Acid No.	H_2SO_4.	HNO_3.	H_2O.	H_2SO_4.	HNO_3.	H_2O.	Calculated moles of NO_2^+/l.
1	75·0	15·0	10·0	0·489	0·152	0·359	0·60
2	80·6	9·85	9·6	0·543	0·103	0·354	0·72
3	85·4	5·06	9·5	0·590	0·054	0·356	0·62
4	87·3	3·94	8·8	0·618	0·043	0·338	0·64
5	87·5	3·71	8·75	0·621	0·041	0·338	0·61
6	93·6	2·0	4·4	0·776	0·026	0·198	0·58

above. The experimental measurements of Chédin (*Mem. des Services chimiques de l'Etat*, 1944, **31**, 113), interpreted according to our views, give results of the same order and equally consistent except for acid No. 6. Such acids might be expected to have equal nitrating powers. This leaves out of account, however, the two-phase nature of the system, and the fact that the concentrations in the acid phase, where nitration takes place, must differ slightly from those in the nitrating acid selected.

When a wide range of nitration data are re-examined in relation to the water mole-fraction in the acid used it appears from Fig. 2, in which the extent of nitration is plotted against the water mole-fraction, that with acids of 5% nitric acid and upwards the rate of nitration varies in a linear manner with varying water mole-fraction, independently of wide variations in the concentration of nitric acid present.

It may be pointed out that acids of the same water mole-fraction are acids of nearly equal water/sulphuric acid ratios since the mole-fraction of sulphuric acid in them does not vary much. In fact, if the nitric acid present is increased while the water mole-fraction is kept constant, a slightly lower H_2O/H_2SO_4 ratio must result and the relationship shown in Fig. 2 may arise from a compensation in the ionisation equilibrium between a somewhat diminished proportion of free sulphuric acid and the increased amount of nitric acid present.

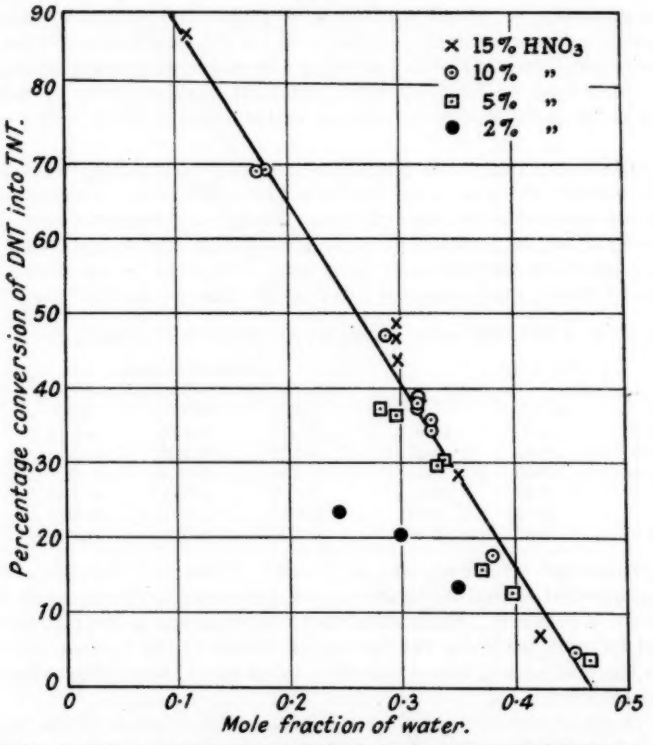
If, on the other hand, we consider the trend of the results of two-phase nitrations in acids of diminishing water content, we find that the nitration rates (using nitrating acids containing 5 or 10% HNO_3) increase steadily as the mole-fraction of water is reduced to zero and show no sign of a maximum for a nitrating acid composed of nitric acid and any aqueous sulphuric acid, comparable with the sharp maximum in homogeneous solutions at 92% H_2SO_4 (H_2O/H_2SO_4 molar ratio = 0·48). There are two reasons which may account for this difference :

(*a*) In two-phase experiments with dinitrotoluene the nitration takes place in the acid

phase. Nitration in the organic phase is negligible, as shown by Mr. W. W. Jones and Mr. A. E. Flood (unpublished observations; compare Hetherington and Masson, *loc. cit.*, who state that no nitration occurs in the nitrobenzene phase, and Lewis and Suen, *Ind. Eng. Chem.*, 1940, **32**, 1095, who found the rate of nitration of benzene to be 5—10 times as fast in the acid phase as in the organic phase). The solubility of dinitrotoluene in the acid phase increases with diminishing water content, and this must at least tend to move the optimum composition for nitration in the direction of acids of lower water content (compare D. I. James, *J.*, 1935, 785).

(*b*) The occurrence of a medium giving a maximum rate for homogeneous nitration depends on the existence of a range of nitrating acids in which an increase in water content accelerates nitration, and this is due to the nearly complete conversion of water and nitric acid into ionic forms by the sulphuric acid in this range. The rising proportion of water therefore increases the concentration of HSO_4^- ion in this region much faster than it diminishes that of the NO_2^+

FIG. 2.



Extent of nitration in 1 *hour at* 100° *of* 50% DNT *in* TNT *mixture with* 2·43 *wts. of mixed acids of various compositions.*

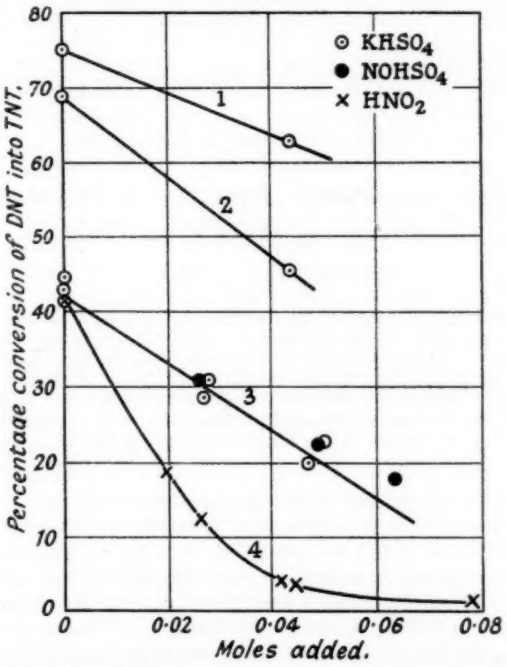
ion. This can only occur, however, when sulphuric acid is present in sufficient molecular excess over both water and nitric acid. In a typical two-phase experiment the nitrating acid was of composition 84·4% H_2SO_4, 9·9% HNO_3, 5·7% H_2O (nitric acid in 93·7% sulphuric acid) and the actual quantities in reaction were : dinitrotoluene 0·0384, sulphuric acid 0·293, nitric acid 0·0538, water 0·108 mole. In this mixture sulphuric acid is in 1·8-fold excess over the nitric acid plus water, as compared with a 4-fold excess in our homogeneous nitration in 96% sulphuric acid. It is readily shown by calculation of the ionic equilibria in these mixtures (discussed in Parts I and IV of this series) that with 5 or 10% of nitric acid present the conversion of the nitric acid into the cationic form NO_2^+ does not approach completeness with any sulphuric acid–water mixture. An examination of the curves from the observations of Chédin (*loc. cit.*) also leads to the same conclusion.

This view is supported by the effect produced on the rate of nitration by the addition of bisulphates.

Effect of Bisulphates and Nitrous Acid.—In Part IV it was shown that the effect of bisulphate

ions in homogeneous nitrations was to accelerate the reaction in the region between the optimum concentration and 100% sulphuric acid but to retard it in acid–water mixtures of less than 92% sulphuric acid. According to our view, the two-phase nitrating mixtures are all effectively analogous to the latter range of media for homogenous nitration, and this requires that bisulphates should always retard the two-phase process. This question has been examined experimentally, for two-phase nitrations with a mixed acid containing 10% of nitric acid, by observing the effect of adding (*a*) potassium bisulphate, (*b*) nitrosyl bisulphate, and (*c*) nitrous acid. The last of these reacts reversibly according to the equation $HNO_2 + 2H_2SO_4 \rightleftharpoons NO^+ + H_3O^+ + 2HSO_4^-$, so that one mole of nitrous acid produces two moles of bisulphate ion and one mole of oxonium ion all capable of affecting the nitric acid ionisation equilibrium.

FIG. 3.



Effects of added substances on extent of nitration at 100°.

Curve 1. 89·1% H_2SO_4: $H_2O/H_2SO_4 = 0·072$. *Nitration for* 30 *mins.*
2. 86·2% H_2SO_4: $H_2O/H_2SO_4 = 0·245$. *Nitration for* 60 *mins.*
3 *and* 4. 81·8% H_2SO_4: $H_2O/H_2SO_4 = 0·563$. *Nitration for* 60 *mins.*
} $HNO_3 = 9·8\%$.

The results of these experiments are shown in Fig. 3. A retardation of the reaction is apparent in all cases. The large retarding effect of bisulphate, shown in the upper two curves, is specially noteworthy since the H_2O/H_2SO_4 ratios for these acids were 0·072 and 0·245, corresponding to points well on the acid side of the optimum velocity point in homogeneous nitrations ($H_2O/H_2SO_4 = 0·48$). This confirms the supposition made above [p. 1188, (*b*)] that, in two-phase nitration, the proportion of nitric acid present is usually too high for its conversion into nitronium ion to be nearly complete.

In this connection it is noteworthy that the nitration of benzoic acid and other substances by means of potassium nitrate and concentrated sulphuric acid (Houben, "Methoden der Organischen Chemie", 3rd edn., 1941, iv, 195) involves essentially homogeneous conditions and that here the reaction is facilitated by the potassium bisulphate formed in solution.

The effects of potassium and nitrosyl bisulphate are not quite equivalent, but the discrepancy is accounted for when allowance is made for the incompleteness of the ionisation reaction of nitrous acid: the substance is 90% ionised in such solutions according to the estimate of Hantzsch and Berger (*Z. anorg. Chem.*, 1930, **190**, 321).

The effect of nitrous acid in depressing the speed of nitration is seen to be more than twice

that of potassium bisulphate, as was to be expected, but here again the result is modified by the reversal of the ionisation equilibrium.

The influence of nitrous acid upon two-phase nitration has made itself felt in another way. If the initial nitrating agent contains too high a proportion of water, nitration stops before the whole of the available reacting material has been consumed. Such an effect, which is similar to the nitration threshold of Hetherington and Masson for nitrobenzene (compare p. 1186), is a natural consequence of the accumulation of water liberated during nitration with a consequent increase of the H_2O/H_2SO_4 ratio to a point where the speed of nitration becomes negligible. But the arrest in the nitration of DNT actually occurs at an earlier stage, because the oxidation processes accompanying the nitration (see Part IV, *loc. cit.*) produce nitrous acid, the retarding action of which is added to that of the water in bringing the reaction to a standstill.

The authors express their thanks to Professor W. E. Garner, F.R.S., in whose laboratory this work was carried out, and to the Director-General of Scientific Research (Defence) for permission to publish.

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224. *β-Cycloylpropionitriles. Part I. A General Synthesis and Conversion into Pyrrole Dyes.*

By EDWARD B. KNOTT.

Cyclyl β-dialkylaminoethyl ketone hydrochlorides, readily obtained by the Mannich reaction, are converted to *β-cycloylpropionitriles* by refluxing with aqueous potassium cyanide. The nitriles on hydrolysis yield *β-cycloylpropionic acids* some of which are not otherwise readily available. β-Benzoylpropionitrile readily absorbs hydrogen chloride to give a crystalline *chloroimide* salt which on treatment with alcohol gives an *alkyl β-benzoylpropimino-ether hydrochloride*. The latter, also formed by the conventional method, gives with hot alcoholic ethyl orthoformate, red 3 : 3′-*pyrromethin* and with β-ethoxyacraldehyde acetal, a blue 3 : 3′-*pyrrotrimethin* dye.

THE preparation of β-cycloylpropionic acids is normally achieved by a Friedel–Crafts condensation of an unsaturated carbocycle or heterocycle with succinic anhydride. This method gives positive results with most suitable carbocyclic and stable heterocyclic compounds. The same acids can also be prepared from the cyclyl bromomethyl ketone by condensation with ethyl sodiomalonate followed by hydrolysis and decarboxylation. Both of these methods fail, however, when the cyclic component is relatively unstable. Thus furan or 2-bromoacetylfuran gave only tars when submitted to either of the above processes. Since β-2-*furoylpropionic acid* was required, an alternative method of preparation was sought.

One method would be by the hydrolysis of β-2-furoylpropionitrile if such a compound were readily available. No general method for the preparation of β-cycloylpropionitriles has been developed, although one such nitrile, β-benzoylpropionitrile (β-cyanopropiophenone) was prepared by Allen, Gilbert, and Young (*J. Org. Chem.*, 1937, **2**, 227) by the addition of hydrogen cyanide to phenyl vinyl ketone.

It is well known (Mannich and Hönig, *Arch. Pharm.*, 1927, **265**, 598) that cyclyl β-dialkylaminoethyl ketones vary in their stability and that many of them, on steam distillation, lose dialkylamine to give cyclyl vinyl ketones. It is also known (Reichert and Posemann, *ibid.*, 1937, **275**, 67) that Mannich salts react with sodionitromethane to give γ-nitrobutyrophenones. It appeared fruitful, therefore, to investigate the action of alkali cyanides on Mannich salts, since such alkalis should release the Mannich bases, and under certain conditions the latter, by loss of dialkylamine followed by hydrogen cyanide addition, might be converted into the desired nitriles.

It has been reported (Mannich and Braun, *Ber.*, 1920, **53**, 1874) that the Mannich salt obtained from *cyclo*hexanone on treatment with aqueous potassium cyanide yields a cyanohydrin of the Mannich base. The β-dialkylaminopropiophenone hydrochlorides (I; R = Ph) which were chosen for model experiments also gave oils on the addition of aqueous potassium cyanide. These are believed to be the cyanohydrins (II; R = Ph) but they readily decomposed on attempted distillation and were not analysed. The product from 2-furyl β-dimethylamino ethyl ketone hydrochloride (I; R = 2-C_4H_3O) and cold aqueous potassium cyanide, however,

was obtained crystalline and found to be **2-*furyl* β-*dimethylaminoethyl ketone cyanohydrin*** (II; R = 2-C_4H_3O, R′ = Me).

$$R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NR'_2,HCl + KCN \longrightarrow R{\cdot}\underset{CN}{\overset{OH}{C}}{\cdot}CH_2{\cdot}CH_2{\cdot}NR'_2 + KCl \longrightarrow R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CN + NHR'_2$$

(I.) (II.) (III.)

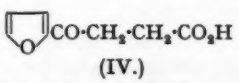
The decomposition of (II; R = Ph), with or without its isolation, was readily brought about by short heating under reflux in water, preferably in the presence of excess alkali cyanide. Dialkylamine was evolved, and β-benzoylpropionitrile formed in reasonably good yield. The yield and the state of purity of the crude product, as well as the optimal reaction time, depended primarily on the concentration of the aqueous cyanide. The greater the dilution the purer was the product, and up to a point the higher the yield. Too great a dilution lowered the yield, owing to the solubility of the nitrile in water. Replacement of water as solvent by aqueous alcohol, and other combinations, always gave lower yields.

The application of this method to other salts (I; R = aryl, or 2-thienyl) gave similar yields of nitrile. β-2-*Furoylpropionitrile* is much more soluble than the other nitriles and must be extracted from the reaction mixture. 2-*Benzfuryl* β-*cyanoethyl ketone* (VI) was also obtained by this method. The reaction appears to be fairly general and the only exception amongst the salts used involved 3-nitro-β-dimethylaminopropiophenone hydrochloride. This salt, the base of which is known to be very unstable, readily releasing amine and formaldehyde (Mannich and Dannehl, *Arch. Pharm.*, 1938, **276**, 206), gave only resins with potassium cyanide. 1-*Naphthyl* β-*dimethylaminoethyl ketone hydrochloride*, which decomposed rapidly on heating in aqueous solution, gave the expected nitrile only when a large excess of cyanide was present.

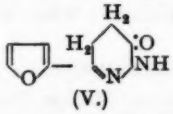
The reaction applied to *p*-chloro-β-dimethylaminopropiophenone hydrochloride gave only a 16·5% yield of the required nitrile and a second solid, analysis of which indicated the empirical formula $C_{19}H_{15}O_3NCl_2$. It formed a monophenylhydrazone and was decomposed to an oil by boiling 18% hydrochloric acid. The simplest substance of this composition, *viz.*, $Cl{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}C(:NH){\cdot}CH{:}CH{\cdot}CO{\cdot}C_6H_4Cl$, would be formed by addition of the intermediate *p*-chlorophenyl vinyl ketone to the *p*-chlorobenzoylpropionitrile, giving 4-imino-1 : 7-diketo-1 : 7-di-*p*-chlorophenylhept-2-ene.

This method of preparation of the nitriles appears to apply only where R′ is alkyl. Such Mannich salts obtained by the substitution of dialkylamines by piperidine or morpholine do not decompose under the conditions employed here. Similarly, Mannich salts from cyclic ketones or propiophenone gave only oils or resins on similar treatment.

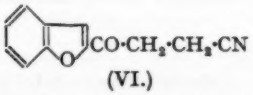
In all cases the nitrile was readily hydrolysed to the β-cycloylpropionic acid (cf. Allen *et al.*, *loc. cit.*). β-2-*Furoylpropionic acid* (IV) resembles β-benzoylpropionic acid in its melting point and physical appearance. It was characterised by its *ethyl* ester and its conversion into 3-*keto*-6-(2′-*furyl*)-2 : 3 : 4 : 5-*tetrahydropyridazine* (V) by hydrazine hydrate.



(IV.)



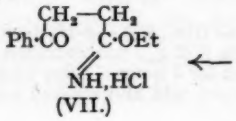
(V.)



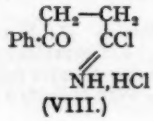
(VI.)

On treating an alcoholic solution of β-benzoylpropionitrile with hydrogen chloride, *ethyl* β-*benzoylpropimino-ether hydrochloride* (VII) was obtained, the *base* of which is crystalline but not very stable; (VII) was also obtained by treating the nitrile with hydrogen chloride in dry benzene and dissolving the resulting, crystalline *chloroimide* salt (VIII) in ethyl alcohol. The chloroimide fumed strongly in air, slowly releasing hydrogen chloride to give the original nitrile. It was decomposed by water to give chiefly the original nitrile together with some β-benzoylpropionamide.

On warming (VII) with 18% hydrochloric acid, ethyl β-benzoylpropionate was formed in quantitative yield, whilst its base, on heating with acetic anhydride, gave the expected N-β-*benzoylpropionylacetamide* (IX). The corresponding *imino-ether* salts from β-4-*methoxybenzoylpropionitrile* and β-4-*hydroxybenzoylpropionitrile* are very sensitive to moisture, and on dissolving in 99% alcohol were converted into β-4-*methoxy*- and β-4-*hydroxy-benzoylpropionamides*.



(VII.)



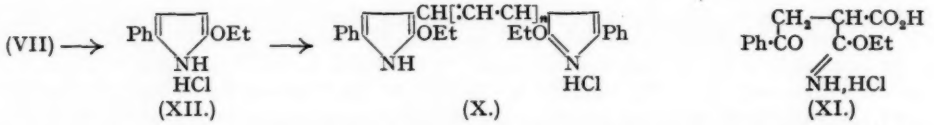
(VIII.)

$Ph{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}CH_3$

(IX.)

All the imino-ether hydrochlorides showed a strong Ehrlich reaction in warm alcohol, indicating ring closure to pyrrole derivatives. The latter could not be isolated, although a yellow crystalline substance together with ammonium chloride was formed on refluxing (VI) in absolute alcohol. Its constitution was not determined.

On refluxing (VII) with alcoholic ethyl orthoformate a brilliant red dye was formed. Analysis suggested the empirical formula $C_{25}H_{25}O_2N_2Cl$ which is the *hydrochloride* of a *base* $C_{25}H_{24}O_2N_2$. Since it is apparent that pyrrole ring formation occurs on heating (VII) in alcohol, the dye is therefore *bis*-3-(2-*ethoxy*-5-*phenylpyrrole*)*methin hydrochloride* (X; $n = 0$) or the *bis*-4-*isomer*. The 3-position of the methin bridge was established with a fair amount of certainty by preparing the imino-ether of α-cyano-β-benzoylpropionic acid (XI) and treating it with *p*-dimethylaminobenzaldehyde and also with ethyl orthoformate. Although (XI), obtained as an oil, was not purified, it gave a strong Ehrlich reaction but no dye with ethyl orthoformate. Since the 3-position in the potential pyrrole ring is blocked by the carboxyl



(XII.) (X.) (XI.)

group it follows that the reaction with *p*-dimethylaminobenzaldehyde must take place in the 4-position, and that either steric hindrance or lower activity of the 4-position precludes dye formation with ethyl orthoformate.

Analogues of (X) were prepared from *methyl* β-*benzoylpropimino-ether hydrochloride* and *ethyl* β-4-*methoxybenzoylpropimino-ether hydrochloride*. The salt (VII) and β-ethoxyacraldehyde acetal gave a blue dye which by analogy is *bis*-3-(2-*ethoxy*-5-*phenylpyrrole*)*trimethin hydrochloride* (X; $n = 1$). The formation of these dyes is interesting. It appears that the initial step of pyrrole ring formation occurs on warming in alcohol; the 2-ethoxy-5-phenylpyrrole hydrochloride (XII) thus formed probably decomposes rapidly to ammonium chloride and the above-mentioned yellow crystalline substance; in the presence of *p*-dimethylaminobenzaldehyde, ethyl orthoformate or β-ethoxyacraldehyde acetal, however, dye formation, occurring immediately the pyrrole ring has formed, stabilises the rings. This stability may be connected with the resonance of the new systems.

Degradation experiments failed to give any simpler pyrrole derivatives. The dye salts are stable in aqueous alcoholic solution at pH 3 but are readily hydrolysed by water at higher pH values. On the addition of alkali to the aqueous-alcoholic solution of the dye, the intense red colour, lost on initial hydrolysis of the salt, is restored; this must be due to salt formation although the identity of the absorption curves indicates no great structural change.

The blue dye (X; $n = 1$) weakly sensitised a photographic silver chloride emulsion at low pH values with a broad maximum sensitivity at 5000—6000 A. extending to 7000 A.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss, Oxford; m. p.s are uncorrected.)

1-*Naphthyl* β-*Dimethylaminoethyl Ketone Hydrochloride* (I; R = 1-$C_{10}H_7$).—1-Naphthyl methyl ketone (85 g.), dimethylamine hydrochloride (42 g.), paraformaldehyde (22·5 g.), concentrated hydrochloric acid (1 c.c.), and ethyl alcohol (150 c.c.) were heated under reflux for 4 hours, poured into acetone (800 c.c.), and chilled. Colourless crystals (45 g.; 34%) were obtained which formed colourless prisms, m. p. 165°, from ethyl alcohol (Found: N, 4·9. $C_{15}H_{18}ONCl$ requires N, 5·3%).

β-*Dimethylamino*-3-*hydroxypropiophenone Hydrochloride* (I; R = 3-OH·C_6H_4).—*m*-Hydroxyacetophenone (50 g.), dimethylamine hydrochloride (40 g.), paraformaldehyde (14·4 g.), concentrated hydrochloric acid (1·5 c.c.), and ethyl alcohol (100 c.c.) were heated under reflux for 1 hour. The *salt* had then partly crystallised. It (44·2 g.; 52·5%) was collected when cold and formed long, fine needles, m. p. 176°, after two recrystallisations from ethyl alcohol (Found: N, 6·1. $C_{11}H_{16}O_2NCl$ requires N, 6·1%).

β-*Dimethylamino*-3-*methoxypropiophenone Hydrochloride* (I; R = 3-MeO·C_6H_4).—*m*-Methoxyacetophenone (23·5 g.), dimethylamine hydrochloride (16·6 g.), paraformaldehyde (6·3 g.), concentrated hydrochloric acid (0·3 c.c.), and ethyl alcohol (50 c.c.) were heated under reflux for 2 hours. The clear liquor was poured into acetone (400 c.c.), and the required *salt* (23 g.; 60·5%) obtained on scratching. It formed cream needles, m. p. 160°, from ethyl alcohol (Found: N, 5·55. $C_{12}H_{18}O_2NCl$ requires N, 5·75%).

β-*Dimethylamino*-4-*hydroxypropiophenone Hydrochloride* (I; R = 4-OH·C_6H_4).—*p*-Hydroxyacetophenone (25 g.), dimethylamine hydrochloride (20 g.), paraformaldehyde (7·2 g.), concentrated hydrochloric acid (0·75 c.c.), and ethyl alcohol (30 c.c.) were heated under reflux for 1 hour. After 10 minutes a mass of crystals had separated. They (32 g.; 76%) were collected when cold and washed with cold

ethyl alcohol. A sample was obtained as glistening plates, m. p. 192°, from ethyl alcohol, in which it is sparingly soluble (Found : N, 6·2; Cl, 15·2. $C_{11}H_{16}O_2NCl$ requires N, 6·1; Cl, 15·45%).

4-Bromo-β-dimethylaminopropiophenone Hydrochloride (I; R = 4-BrC_6H_4).—*p*-Bromoacetophenone (25 g.), dimethylamine hydrochloride (12 g.), paraformaldehyde (4·5 g.), concentrated hydrochloric acid (0·5 c.c.), and ethyl alcohol (30 c.c.) were refluxed together for 2 hours, then chilled, and acetone (50 c.c.) added; the *salt* (17·9 g.; 49%) crystallised, and formed jagged needles, m. p. 196°, from ethyl alcohol (Found : N, 4·7. $C_{11}H_{15}ONClBr$ requires N, 4·8%).

2-Benzfuryl β-Dimethylaminoethyl Ketone Hydrochloride (I; R = 2-*benzfuryl*).—2-Acetylbenzfuran (34 g.) (Stoermer and Schäffer, *Ber.*, 1903, **36**, 2863), dimethylamine hydrochloride (17·3 g.), paraformaldehyde (7·2 g.), and ethyl alcohol (100 c.c.) were refluxed together for 2 hours. The clear solution was concentrated to half its volume, acetone (200 c.c.) added, and the mixture chilled. The crystals (21 g.; 39%) were washed with acetone and obtained as tiny needle rosettes (Found : N, 5·15; Cl, 13·5. $C_{13}H_{16}O_2NCl$ requires N, 5·5; Cl, 14·0%), m. p. 188°, from ethyl alcohol. The filtrates gave unchanged acetylbenzfuran (16·5 g.) on dilution with water.

α-Dimethylaminomethylpropiophenone Hydrochloride.—Propiophenone (134 g.), dimethylamine hydrochloride (106 g.), paraformaldehyde (40 g.), concentrated hydrochloric acid (2 c.c.) and ethyl alcohol (160 c.c.) were heated under reflux for 2 hours. After cooling, ether was added to precipitate an oil, which solidified on shaking (184 g.; 81%). It formed tiny needles, m. p. 142·5°, from ethyl alcohol–ether (Found : N, 6·35. $C_{12}H_{18}ONCl$ requires N, 6·15%).

β-Benzoylpropionitrile (III; R = Ph).—(*a*) β-Dimethylaminopropiophenone hydrochloride (213·5 g.; 1 mol.) (*Org. Synth.*, **23**, 30) and potassium cyanide (130 g.; 2 mols.) were placed in a flask and boiling water (2600 c.c.) added rapidly. The whole, consisting of an aqueous and an oily layer, was refluxed for 30 minutes. Part of the dimethylamine distilled and was collected in an dilute hydrochloric acid. On chilling, the oil crystallised, and crystals formed from the aqueous layer. The nitrile (67% yield) formed almost colourless blades, m. p. 76°, from benzene–light petroleum (Found : C, 75·2; H, 5·85; N, 8·6. Calc. for $C_{10}H_9ON$: C, 75·5; H, 5·65; N, 8·8%). Allen *et al.* (*loc. cit.*) give m. p. 76° from ethyl alcohol.

(*b*) Crude β-diethylaminopropiophenone hydrochloride contaminated with diethylamine hydrochloride (900 g.) was obtained by refluxing for 2 hours a mixture of acetophenone (422 g.), diethylamine hydrochloride (500 g.), paraformaldehyde (138 g.), concentrated hydrochloric acid (7 c.c.), and ethyl alcohol (280 c.c.) and adding dry ether to the cooled reaction mixture until no more solid precipitated. The crude salt (24·1 g.), potassium cyanide (13 g.), and boiling water (520 c.c.) were refluxed for 20 minutes, and the nitrile, m. p. 76°, isolated and purified as under (*a*). The yield of nitrile was 48% based on the diethylamine hydrochloride.

β-p-Toluoylpropionitrile (II; R = *p*-MeC_6H_4).—β-Dimethylamino-4-methylpropiophenone hydrochloride (22·7 g.; 0·1 mol.), potassium cyanide (13·0 g.; 0·2 mol.), and boiling water (520 c.c.) were refluxed for 20 minutes. The crystalline *nitrile* (9·0 g.; 52%) obtained on chilling formed glossy needles, m. p. 76°, from ethyl alcohol (Found : N, 8·15. $C_{11}H_{11}ON$ requires N, 8·2%).

β-p-Chlorobenzoylpropionitrile (II, R = *p*-ClC_6H_4).—*p*-Chloro-β-dimethylaminopropiophenone hydrochloride (124 g.) (Dhont and Wibaut, *Rec. Trav. chim.*, 1944, **63**, 81), potassium cyanide (65 g.), and boiling water (2600 c.c.) were refluxed together for 30 minutes. On chilling, the oil solidified. It was washed, and dissolved in ethyl alcohol. On cooling, the *nitrile* (16 g., 16·5%) crystallised. It formed flat, colourless needles, m. p. 72·5°, from ethyl alcohol (Found : N, 7·35. $C_{10}H_8ONCl$ requires N, 7·25%). The primary filtrate on prolonged standing gave a second solid (18·0 g.) which was obtained as fine white needles, m. p. 115°, from ethyl alcohol (Found : C, 63·35; H, 4·3; N, 3·95; Cl, 19·45. $C_{19}H_{16}O_2NCl_2$ requires C, 63·35; H, 4·15; N, 3·9; Cl, 19·7%). Its *monophenylhydrazone* formed pale yellow, feathery needles, m. p. 146—148°, from alcohol (Found : N, 8·95. $C_{25}H_{21}ON_3Cl_2$ requires N, 9·35%). The filtrates from the second crystallisation, on concentration, gave a further crop of nitrile (14·4 g.), m. p. 72·5°, so the total yield of the required nitrile was 31·5%. It was readily hydrolysed to β-*p*-chlorobenzoylpropionic acid, m. p. 134° (Skraup and Schwamberger, *Annalen*, 1928, **462**, 135, give m. p. 134°).

β-p-Bromobenzoylpropionitrile (II; R = *p*-BrC_6H_4).—*p*-Bromo-β-dimethylaminopropiophenone hydrochloride (14·6 g.), potassium cyanide (6·5 g.), and boiling water (130 c.c.) were refluxed for 20 minutes. On chilling, the oil crystallised. The *nitrile* (7·2 g.; 62·5%) formed tiny needles, m. p. 81°, from ethyl alcohol (Found : N, 5·65. $C_{10}H_8ONBr$ requires N, 5·9%).

β-p-Bromobenzoylpropionic Acid.—The nitrile (1 g.) was refluxed for 1 hour with concentrated hydrochloric acid (10 c.c.), and the *acid* which crystallised on cooling was dissolved in aqueous sodium carbonate, and the solution filtered and acidified. The acid formed colourless needles, m. p. 148°, from water (Found : Br, 31·2. $C_{10}H_9O_3Br$ requires Br, 31·1%).

β-3-Hydroxybenzoylpropionitrile; (III; R = 3-OH·C_6H_4).—β-Dimethylamino-3-hydroxypropiophenone hydrochloride (41 g.), potassium cyanide (23·2 g.), and boiling water (900 c.c.) were refluxed for 30 minutes. The chilled liquor gave on acidification with acetic acid an oil which slowly solidified. It crystallised as needles, m. p. 98°, from aqueous alcohol (Found : N, 8·2. $C_{10}H_9O_2N$ requires N, 8·0%). The *acid*, obtained by refluxing the *nitrile* (2 g.) with 18% hydrochloric acid (20 c.c.), for 1 hour, formed irregular plates, m. p. 146·5°, from water (Found : C, 61·75; H, 5·0. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·15%).

β-4-Hydroxybenzoylpropionitrile (III; R = 4-OH·C_6H_4).—Prepared as for the 3-isomer, this *nitrile* was precipitated as a crystalline solid on the addition of acetic acid to the reaction mixture. It was obtained as colourless, flat needles, m. p. 162°, from a little ethyl alcohol in 59% yield (Found : C, 68·35; H, 5·35; N, 7·95. $C_{10}H_9O_2N$ requires C, 68·55; H, 5·15; N, 8·0%). The acid formed colourless needles, m. p. 157°, from hot water. Fieser *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 2966) give m. p. 154—156° (Found : C, 61·55; H, 5·05. Calc. for $C_{10}H_{10}O_4$: C, 61·85; H, 5·15%).

β-3-Methoxybenzoylpropionitrile (III; R = 3-MeO·C_6H_4).—β-Dimethylamino-3-methoxypropiophenone hydrochloride (12·2 g.; 0·05 mol.), potassium cyanide (13 g.; 0·2 mol.), and boiling water (520 c.c.) were refluxed for 10 minutes. On chilling, the oil crystallised. It formed colourless needles, m. p. 54°,

in 73% yield from methyl alcohol by repeated concentration of the filtrates (Found: N, 7·2. $C_{11}H_{11}O_2N$ requires N, 7·4%). The *acid* was obtained on hydrolysis of the *nitrile* with 18% hydrochloric acid as colourless needles, m. p. 108°, from water (Found: C, 63·2; H, 5·95. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·75%).

β-4-Methoxybenzoylpropionitrile (III; R = 4-MeO·C_6H_4).—β-Dimethylamino-4-methoxypropiophenone hydrochloride (24·35 g.; 0·1 mol.), obtained in 86% yield by the method given for the unsubstituted product (*Org. Synth.*, **23**, 31) (cf. Mannich and Lammering, *Ber.*, 1922, **55**, 3510), potassium cyanide (13·0 g.; 0·2 mol.), and boiling water (520 c.c.) were refluxed for 20 minutes and chilled. The *nitrile* was obtained as glassy needles, m. p. 95°, from ethyl alcohol in 71% yield (Found: C, 69·6; H, 5·7; N, 7·65. $C_{11}H_{11}O_2N$ requires C, 69·85; H, 5·8; N, 7·4%). The acid had m. p. 144°, alone, and mixed with a specimen prepared from anisole and succinic anhydride (Poppenberg, *Ber.*, 1901, **34**, 5257).

β-3 : 4-Dimethoxybenzoylpropionitrile [II, R = $(MeO)_2C_6H_3$].—β-Dimethylamino-3 : 4-dimethoxypropiophenone hydrochloride (21 g.) (Mannich and Lammering, *loc. cit.*), potassium cyanide (10 g.), and boiling water (400 c.c.) were refluxed for 20 minutes. The *nitrile* (13·3 g., 85%) was obtained as glassy needles, m. p. 118°, from ethyl alcohol (Found: N, 6·5. $C_{12}H_{13}O_3N$ requires N, 6·4%).

β-1-Naphthoylpropionitrile (III; R = 1-$C_{10}H_7$).—1-Naphthyl β-dimethylaminoethyl ketone hydrochloride (5 g.; 1 mol.), potassium cyanide (5·0 g.; 4 mols.), and boiling water (200 c.c.) were refluxed for 30 minutes. The solid obtained on chilling (1·7 g.; 42·5%) formed tiny needle rosettes, m.p. 113—114°, from methyl alcohol (Found: C, 79·8; H, 5·3; N, 6·9. $C_{14}H_{11}ON$ requires C, 80·4; H, 5·25; N, 6·7%).

β-2-Naphthoylpropionitrile (III; R = 2-$C_{10}H_7$).—2-Naphthyl β-dimethylaminoethyl ketone hydrochloride (50 g.) (Blicke and Maxwell, *J. Amer. Chem. Soc.*, 1942, **64**, 431), potassium cyanide (50 g.), and boiling water (1 l.) were refluxed for 30 minutes. The *nitrile* (15·1 g., 38%), obtained on chilling, formed clusters of yellow needles, m. p. 114°, from ethyl alcohol (Found: N, 6·65%).

2-Furyl β-Dimethylaminoethyl Ketone Cyanohydrin (II; R = 2-C_4H_3O, R′ = Me).—2-Furyl β-dimethylaminoethyl ketone hydrochloride (8·15 g.; 0·04 mol.) (Levvy and Nisbet, *J.*, 1938, 1055) was dissolved in cold water (5 c.c.), and a solution of potassium cyanide (5·2 g.; 0·08 mol.) in water (10 c.c.) added. Colourless crystals of the *cyanohydrin* separated. It formed colourless needles, m. p. 45°, from ligroin (Found: C, 62·2; H, 7·2; N, 14·3. $C_{10}H_{14}O_2N_2$ requires C, 62·0; H, 7·2; N, 14·45%).

β-2-Furoylpropionitrile (III; R = 2-C_4H_3O).—2-Furyl β-dimethylaminoethyl ketone hydrochloride (81·5 g.; 0·4 mol.), potassium cyanide (52 g.; 0·8 mol.), and boiling water (2850 c.c.) were refluxed for 30 minutes, and the clear orange liquor was cooled and extracted 4 times with chloroform (100 c.c.). The dried (Na_2SO_4) extract was freed from chloroform to give a brown oil (32 g.; 57%) which crystallised completely. It formed colourless needles, m. p. 74—76°, from ethyl alcohol after treatment with charcoal (Found: C, 64·65; H, 4·65; N, 9·45. $C_8H_7O_2N$ requires C, 64·5; H, 4·7; N, 9·4%).

β-2-Furoylpropionic Acid (IV).—The nitrile (2 g.) was refluxed for 1 hour with 18% hydrochloric acid (20 c.c.), charcoal was added, and after a further 10 mins.' refluxing the liquor was diluted with water (50 c.c.), filtered, and the light yellow solution concentrated. The *acid* (2·1 g., 93%) separated as yellow grains. It had m. p. 115° and was pure. On recrystallising from hot water it was obtained as almost colourless, glistening flakes, m. p. 115°, lowered to 106° with previous softening on repeated crystallisation (Found: C, 57·25; H, 4·75. $C_8H_8O_4$ requires C, 57·15; H, 4·75%).

The acid (2 g.) was boiled for 15 minutes with 10% ethyl-alcoholic sulphuric acid (10 c.c.), cooled, and poured into water. The precipitated oil crystallised rapidly. The *ethyl* ester formed glistening, colourless plates, m. p. 52—53°, from aqueous alcohol (Found: C, 61·05; H, 5·95. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%).

3-Keto-6-(2′-furyl)-2 : 3 : 4 : 5-tetrahydropyridazine (V).—β-2-Furoylpropionic acid (1·68 g.; 0·01 mol.), aqueous hydrazine hydrate (1 c.c. of 85%), and ethyl alcohol (5 c.c.) were refluxed for 1 hour, then diluted with water (100 c.c.). The *pyridazone* which separated formed yellow, glassy needles, m. p. 145°, from ethyl alcohol (Found: C, 58·8; H, 4·7; N, 17·0. $C_8H_8O_2N_2$ requires C, 58·55; H, 4·9; N, 17·1%).

β-2-Thienoylpropionitrile (III; R = 2-C_4H_3S).—2-Thienyl β-dimethylaminoethyl ketone hydrochloride (2·2 g.; 0·01 mol.) (Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 453), potassium cyanide (1·3 g.; 0·02 mol.), and boiling water (52 c.c.) were heated under reflux for 20 minutes. On cooling, the *nitrile* (67% yield) crystallised. It formed colourless needles, m. p. 66°, from benzene–light petroleum (Found: N, 8·4; S, 19·2. C_8H_7ONS requires N, 8·5; S, 19·45%). The acid, obtained on hydrolysis of the nitrile, formed flat needles, m. p. 120°, alone, and mixed with a specimen prepared from thiophen and succinic anhydride (Fieser and Kenelly, *J. Amer. Chem. Soc.*, 1935, **57**, 1615) (Found: S, 17·3. Calc. for $C_8H_8O_3S$: S, 17·4%).

2-Benzfuryl β-Cyanoethyl Ketone (VI).—2-Benzfuryl β-dimethylaminoethyl ketone hydrochloride (5·07 g.), potassium cyanide (5·2 g.), and boiling water (130 c.c.) were refluxed for 10 minutes. The hot aqueous layer was decanted from an oil which thickened on chilling. The chilled aqueous layer deposited a mass of crystals which formed colourless needles, m. p. 110—111°, after repeated recrystallisation from methyl alcohol, in 21% yield. The oil was not investigated further (Found: N, 6·9. $C_{12}H_9O_2N$ requires N, 7·05%). The *acid* formed faintly yellow needles, m. p. 148°, from hot water (Found: C, 65·75; H, 4·55. $C_{12}H_{10}O_4$ requires C, 66·05; H, 4·6%).

Chloroimide from β-Benzoylpropionitrile (VIII).—The nitrile (10 g.) and dry benzene (50 c.c.) were cooled in ice, and a rapid stream of dry hydrogen chloride passed into the suspension. The solid dissolved, and crystals soon commenced to separate. After 30 minutes the solid was collected, washed with dry ether, and dried rapidly in a vacuum. The *chloroimide* salt (7·2 g.) formed pale yellow leaflets, m. p. 99° (efferv.) (Found, for the freshly prepared substance: C, 52·0; H, 4·95; N, 6·35; Cl, 29·6. $C_{10}H_{11}ONCl_2$ requires C, 51·75; H, 4·75; N, 6·05; Cl, 30·55%). On standing over aqueous potassium hydroxide for 14 days the original nitrile, m. p. 76°, was recovered.

Ethyl β-Benzoylpropimino-ether Hydrochloride (VII).—(*a*) The nitrile (25 g.) was suspended in ethyl alcohol (50 c.c.), and a rapid stream of dry hydrogen chloride was passed into the suspension cooled in ice. The temperature rose to 40°, the solid dissolved, and a deep yellow colour developed. When

saturated, the solution was left to stand for 1 hour, and the *salt* was precipitated by addition of dry ether. It formed colourless needles, m. p. 130°, in 60% yield after recrystallisation from cold ethyl alcohol–ether. The yield was not improved by keeping the reaction temperature below 10° (Found: C, 58·95; H, 6·7; N, 5·95; Cl, 14·55. $C_{12}H_{16}O_2NCl$ requires C, 59·5; H, 6·65; N, 5·8; Cl, 14·7%).

(*b*) The chloroimide hydrochloride (VIII) was dissolved in a minimum of hot ethyl alcohol, chilled immediately, and (VII) precipitated as colourless needles, m. p. 130°, by the addition of ether.

The *base* was obtained as an oil on adding aqueous sodium carbonate to an aqueous solution of the salt. It solidified rapidly and was obtained as colourless, glassy crystals, m. p. 60°, from light petroleum. The crystals turned magenta on keeping (Found: C, 70·4; H, 7·2; N, 7·05. $C_{12}H_{15}O_2N$ requires C, 70·5; H, 7·2; N, 6·85%).

Methyl β-Benzoylpropimino-ether Hydrochloride.—This *salt* was obtained from (VIII), in the same way as the ethyl homologue, by using methyl alcohol as solvent. It formed colourless needles, m. p. 127°, from methyl alcohol–ether (Found: Cl, 15·55. $C_{11}H_{14}O_2NCl$ requires Cl, 15·6%).

Ethyl β-4-Methoxybenzoylpropimino-ether Hydrochloride.—β-4-Methoxybenzoylpropionitrile (5 g.) and ethyl alcohol (10 c.c.) were treated with dry hydrogen chloride whilst cooling in ice. Precipitation of the salt commenced after a short time and was completed by addition of dry ether. It (5·5 g., 77%) was dissolved in absolute alcohol, the solution saturated with hydrogen chloride, and the *salt* reprecipitated by ether. It formed colourless needles, m. p. 133° (effervescence) (Found: Cl, 12·1. $C_{13}H_{18}O_3NCl$ requires Cl, 13·1%). On dissolving the salt in alcohol containing 1% water, *β-4-methoxybenzoylpropionamide* separated. It formed glistening plates or flat needles, m. p. 136°, from ethyl alcohol (Found: C, 63·95; H, 6·2; N, 6·55. $C_{11}H_{13}O_3N$ requires C, 63·75; H, 6·35; N, 6·75%).

β-4-Hydroxybenzoylpropionamide.—The imino-ether hydrochloride prepared analogously from β-4-hydroxybenzoylpropionitrile was dissolved in ethyl alcohol containing 1% of water, and on cooling the *amide* separated. It formed colourless irregular crystals, m. p. 218° (blue at 210°), from ethyl alcohol (bluish solution) (Found: N, 7·8. $C_{10}H_{11}O_3N$ requires N, 7·5%).

Decomposition of (VII).—(*a*) The hydrochloride (VII) (3·9 g.) was refluxed in absolute alcohol (20 c.c.) for 30 minutes. The solution turned orange, and ammonium chloride (0·4 g.) separated. On concentration a further crop (0·2 g.) separated. This represented 70% of the total nitrogen. The residue gave an oil on dilution with water, which solidified almost completely. It formed long, orange needles, m. p. 150° (0·6 g.), from ethyl alcohol (Found: C, 76·0; H, 6·1; N, 4·9%).

(*b*) The same hydrochloride (10 g.) was dissolved in concentrated hydrochloric acid (10 c.c.) and water (20 c.c.), and warmed on the steam-bath. The oil which slowly separated was taken up in ether, dried, and distilled. It (7·5 g.) had b. p. 165°, and was ethyl β-benzoylpropionate (Found: C, 69·6; H, 7·0. Calc. for $C_{12}H_{14}O_3$: C, 70·0; H, 6·8%).

N-*β-Benzoylpropionylacetamide* (IX).—Ethyl β-benzoylpropimino-ether (1 g.) and acetic anhydride (10 c.c.) were heated for 2 hours on the steam-bath. On decomposition with water, an oil was obtained which partly crystallised. It formed colourless, silky needles, m. p. 139—140°, from ethyl alcohol (Found: C, 65·9; H, 6·0; N, 6·3. $C_{12}H_{13}O_3N$ requires C, 65·75; H, 5·95; N, 6·4%).

Bis-3-(2-ethoxy-5-phenylpyrrole)methin Hydrochloride (X; $n = 0$).—Ethyl β-benzoylpropimino-ether hydrochloride (4·83 g.; 0·02 mol.), ethyl orthoformate (5·92 g.; 0·04 mol.), and 99% ethyl alcohol (10 c.c.) were refluxed for 15 minutes, by which time the whole had solidified to a mass of red needles. From ethyl alcohol this formed bright red needles, m. p. 175—176°, turning bronze on contact with air (Found: C, 71·2; H, 5·9; N, 6·95; Cl, 8·65. $C_{25}H_{23}O_2N_2Cl$ requires C, 71·5; H, 5·95; N, 6·65; Cl, 8·45%). Its absorption maximum in methyl alcohol lies at 4700 A. After standing in contact with moist air for 48 hours it shows no absorption peak. Its sodium hydroxide–methyl alcohol solution also give a maximum absorption at 4700 A. and an absorption curve almost identical with that of the freshly prepared dye in neutral or acid solution. The mother-liquor, freed from *dye*, deposited yellow needles, m. p. 150°, identical with the product obtained by heating the starting material in ethyl alcohol.

Bis-3-(2-methoxy-5-phenylpyrrole)methin Hydrochloride.—Prepared in the same way as the ethoxy-analogue, but with methyl alcohol as solvent, the *dye* formed red needles, m. p. 176° (for the freshly prepared substance; 163—164°, after standing in air for 1 hour), on recrystallisation from methyl alcohol (Found: Cl, 9·0. $C_{23}H_{21}O_2N_2Cl$ requires Cl, 9·05%).

Bis-3-(2-ethoxy-5-4′-methoxyphenylpyrrole)methin Hydrochloride.—Ethyl β-4-methoxybenzoylpropimino-ether hydrochloride (2·7 g.), ethyl orthoformate (3·0 g.), and ethyl alcohol (25 c.c.) were refluxed for 30 minutes. The red solution had, by this time, become brown, owing to complete crystallisation of the *dye*. It is very insoluble and was purified by boiling with *n*-butyl alcohol for 15 minutes and collecting whilst hot. It formed green crystals, m. p. 266° (Found: N, 6·05; Cl, 7·65. $C_{27}H_{25}O_4N_2Cl$ requires N, 5·8; Cl, 7·35%).

Bis-3-(2-ethoxy-5-phenylpyrrole)trimethin Hydrochloride (X; $n = 1$).—Ethyl β-benzoylpropimino-ether hydrochloride (2·4 g.; 2 mols.), β-ethoxyacraldehyde acetal (0·8 g.; 1 mol.), and ethyl alcohol (10 c.c.) were refluxed for 10 minutes. The blue solution had then deposited crystals of the *dye*. They (0·4 g.) were collected after cooling and obtained as green crystals, m. p. 162°, from ethyl alcohol (Found: C, 72·65; H, 6·05; N, 6·0; Cl, 7·55. $C_{27}H_{27}O_2N_2Cl$ requires C, 72·55; H, 6·05; N, 6·25; Cl, 7·95%). In moist methyl alcohol the dye shows a maximum absorption at 4750—4800 A.; in methyl alcohol containing a little concentrated hydrochloric acid the maximum lies at 6050 A.; in methyl alcohol containing a little aqueous sodium hydroxide the maximum is also at 6050 A. but fades rapidly.

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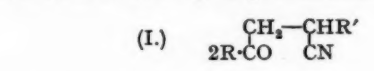
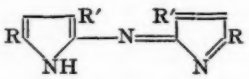
225. *β-Cycloylpropionitriles. Part II. Conversion into Bis-2-(5-cyclylpyrrole)azamethin Salts.*

By Edward B. Knott.

The blue dyes obtained by heating β-cycloylpropionitriles with hydroxylamine salts are *salts* of bis-2-(5-cyclylpyrrole)azamethin (II; R = cyclyl, R′ = H). One of the dyes (II; R = Ph, R′ = H) was also prepared from α-cyano-β-benzoylpropionic acid and hydroxylamine hydrochloride. Bis-2-(3 : 5-diphenylpyrrole)azamethin (II; R = R′ = Ph) (Rogers, *J.*, 1943, 590) was prepared similarly from β-benzoyl-α-phenylpropionitrile. The new dyes exhibit remarkable colour reactions with concentrated sulphuric acid.

The remarkable stability of the 2-bis-(3 : 5-diarylpyrrole)azamethins (II; R = R′ = aryl), discovered by Rogers (*loc. cit.*; B.P. 544,101) and less accurately named 2 : 2′ : 4 : 4′-tetraaryldipyrroazamethins by him, prompted the search for similarly constituted products, simpler in nature and of higher general solubility.

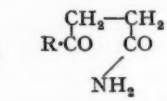
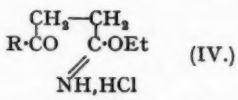
(I.)  (II.) 

One of the methods employed by Rogers for the preparation of the above dyes consisted in heating β-aroyl-α-arylpropionitriles (I; R, R′ = aryl) with ammonium formate in the presence of air, whilst Davies and Rogers (*J.*, 1944, 126) heated the same nitriles with formamide to obtain formylated 2-amino-3 : 5-diarylpyrroles, which can be used as intermediates for the above dyes. Although Rogers had not treated the simple β-aroylpropionitriles (I; R = aryl, R′ = H) with either reagent in the expectation of obtaining dyes (II; R = aryl, R′ = H), he had found that γ-nitrobutyrophenone gave no dye of this type under conditions which, when applied to γ-nitro-β-arylbutyrophenones, gave good yields of dye (II; R, R′ = aryl).

Since a variety of β-cycloylpropionitriles were readily available by the method described in Part I (preceding paper), an investigation of their possible use as intermediates was undertaken.

On heating β-benzoylpropionitrile with ammonium formate in the presence of air at various temperatures, no trace of dye formation could be observed, nor could any formylated 2-amino-5-phenylpyrrole be isolated from a formamide melt. These negative results thus fell into line with the behaviour of γ-nitrobutyrophenone (Rogers, *loc. cit.*). It appeared, therefore, that dye formation required, not only a β-aroyl group in the starting nitrile (where R = Me, R′ = aryl, no dye was formed; Rogers, *loc. cit.*, p. 595), but also an α-substituent (aryl?).

It is known, however (Biedermann, *Ber.*, 1891, **24**, 4071; Tiemann, *ibid.*, p. 4077), that β-benzoylpropionamide (III; R = Ph) shows a tendency on fusion or dissolution to give a blue coloration, and this was also observed (see Part I) on melting or recrystallising β-*p*-hydroxybenzoylpropionamide. It was also noticed that, in attempting to form the amidine from ethyl β-benzoylpropimino-ether hydrochloride (IV; R = Ph) by solution in alcoholic ammonia and also on boiling (IV) with aqueous ammonia, a blue colour developed. There seemed, therefore, the possibility that this colour could be attributed to the formation of dyes of type (II; R′ = H).

(III.)   (IV.)

It is also known (Klobb, *Ann. Chim. Phys.*, 1897, **10**, 184; Bougault, *ibid.*, 1908, **15**, 504) that α-cyano-β-benzoylpropionic acid (I; R = Ph, R′ = CO_2H) gives a blue dye on evaporation of solutions of its salts or on acidification of an alkaline solution of the acid which has been in contact with air. Klobb also reported that the dye could be sublimed with some decomposition, the vapours being red. This stability to heat is possessed to a greater degree by Rogers's dyes. It seemed therefore possible that this dye also might belong to type (II), in which R′ is a carboxyl group.

Attempts to prepare and purify the dyes from (III) or (IV) in sufficient quantities for analysis were unsuccessful, but the dye from (I; R = Ph, R′ = CO_2H) was obtained in a small amount. It was insoluble in strong alkalis, but dissolved in concentrated sulphuric acid to give a pale yellow-green solution which gave blue flocks on pouring into water. In aqueous pyridine it was decolorised by sodium dithionite. It was almost insoluble in most

solvents but dissolved in nitrobenzene or pyridine giving a magenta solution. Analysis suggested the formula $C_{20}H_{14}O_2N_2$ which rules out the possibility of its belonging to the dipyrroazamethin class of dye. It is also readily prepared in low yield from β-benzoylpropionamide by a different method, and the proposed structure and mechanism of formation are discussed later. The non-identity of these dyes with dipyrroazamethins was disappointing, and work on the preparation of (II; R′ = H) was about to be abandoned when, by chance, an unusual reaction was observed. Whilst engaged on the preparation of various derivatives of the β-aroylpropionitriles (I; R′ = H) for their characterisation, difficulty was encountered in the formation of their oximes. Thus, β-benzoylpropionitrile (I; R = Ph, R′ = H) failed to give an oxime with either hydroxylamine acetate or the base itself on refluxing in ethyl alcohol, most of the original nitrile being recovered unchanged. On refluxing an alcoholic solution of the nitrile with hydroxylamine hydrochloride, however, the mixture darkened and a brilliant blue coloration developed. When a large excess of the hydroxylamine salt was employed the dye crystallised during the refluxing, giving an almost solid mass of needles. The dye was slightly soluble in boiling water, the solution giving an immediate precipitation of silver chloride on addition of silver nitrate. It was soluble in alcohols, acetone, and pyridine. Analysis suggested the formula $C_{20}H_{15}N_3,2HCl$. Its alcoholic solution when poured into water gave magenta flocks soluble in alcohol to a blue solution and which on purification gave a second blue dye of the formula $C_{20}H_{15}N_3,HCl$. Attempts to isolate the base were fruitless since, although it had some stability in solution, it readily decomposed on attempted isolation. The *dye salts* were very stable to boiling concentrated hydrochloric acid, dissolved in concentrated sulphuric acid to give a blue solution, and were reduced to a colourless leuco-compound by sodium dithionite. The leuco-compound was reoxidised by aerial oxygen to a blue dye. The salts did not sublime on heating under reduced pressure. Apart from the last property (which might be expected of the salts) the behaviour of these dyes is similar to that of Rogers's dye (II; R = R′ = Ph), and the analysis agrees well with their being the *dihydrochloride* and *monohydrochloride* of bis-2-(5-phenylpyrrole)azamethin (II; R = Ph, R′ = H). Degradation experiments with hydriodic acid, and with an acetic anhydride–sodium acetate mixture which discharged the colour, did not lead to any definite products. Rogers (*loc. cit.*) proved the constitution of his dyes by an alternative synthesis which consisted in the condensation of 3 : 5-diphenylpyrrole with 2-nitroso-3 : 5-diphenylpyrrole. Nitrosation of 2-phenylpyrrole, however, either with nitrous acid or with alkaline amyl nitrite, failed to give a pure nitroso-derivative. The dark green solid obtained when employing nitrous acid gave a magenta dye on heating with 2-phenylpyrrole in acetic anhydride–acetic acid mixtures but not in sufficient quantities for isolation. Since 2-phenylpyrrole is readily converted into a magenta dye in the presence of mineral acids and acetic anhydride, it is possible that the green solid causes dye formation by virtue of its being a hydrochloride. Alternatively, if nitrosation occurs in the β-position, as is usual with pyrroles (cf. Fischer and Orth, " Die Chemie des Pyrrols," Vol. I, p. 104), the interaction of 4-nitroso-2-phenylpyrrole hydrochloride with 2-phenylpyrrole might well lead to a magenta dye. The structure of the dye was proved beyond reasonable doubt, however, by obtaining analogously bis-2-(3 : 5-diphenylpyrrole)azamethin (II; R, R′ = Ph) from β-benzoyl-α-phenylpropionitrile and hydroxylamine hydrochloride. The reaction proceeded best in boiling butanol to give the unstable dye salt, or in ethylene glycol at 120° to give the dye base. It was also found to proceed rapidly to give a low yield of dye on using formamide as solvent. The salt rapidly lost hydrogen chloride on contact with the atmosphere. The base had all the properties of the dye prepared according to Rogers (*loc. cit.*) and analysis confirmed the identity.

The instability of the new dye base may explain the non-formation of dye on heating γ-nitrobutyrophenone and ammonium formate (Rogers, *loc. cit.*), although further attempts at dye formation by this reaction in the presence of salts such as ammonium chloride or hydroxylamine hydrochloride also failed.

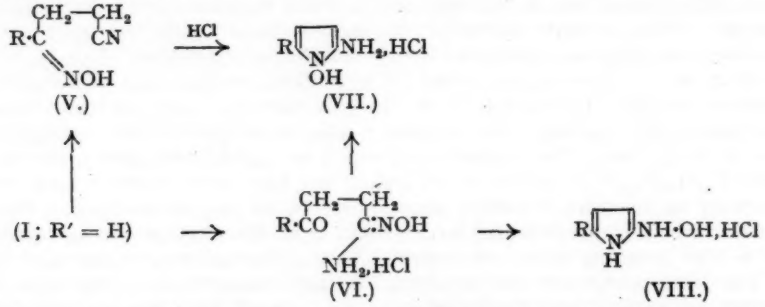
β-Benzoylpropionitrile and hydroxylamine sulphate gave *bis-2-(5-phenylpyrrole)azamethin sulphate.*

The reaction was then applied to a variety of β-cycloylpropionitriles in order to determine its scope. In every case β-aroylpropionitriles gave the required dye. β-2-Thienoylpropionitrile (I; R = 2-C_4H_3S, R′ = H) gave the corresponding dye in low yield, but β-2-furoylpropionitrile and 2-benzfuryl 2-cyanoethyl ketone gave only brown solutions on similar treatment.

On heating α-cyano-β-benzoylpropionic acid (I; R = Ph, R′ = CO_2H) with alcoholic hydroxylamine hydrochloride a blue, alkali-insoluble dye resulted. Its analysis, and physical

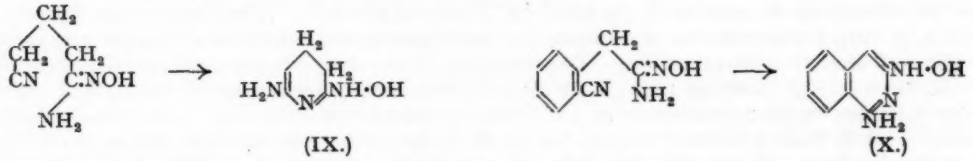
and chemical properties, showed that it was identical with the dye obtained from β-benzoylpropionitrile. The loss of carbon dioxide took place before dye formation occurred, a copious evolution being observed on heating the reactants at 95° in butenol. It is possible that the substituted pyrrole-β-carboxylic acid which may be an intermediate in the dye formation, like other such acids, is readily decarboxylated (cf. Ciamician, *Ber.*, 1880, **13**, 2235; 1881, **14**, 1054).

The mechanism of the reaction is obscure, since no intermediates could be isolated. The first stage reaction could take place in two ways, either by oxime formation (V), or by hydroxylamine addition to the nitrile group to give an amidoxime (VI). At this stage, cyclisation in two ways might occur to give either 2-amino-1-hydroxy-5-R-pyrrole (VII) or 2-hydroxylamino-5-R-pyrrole (VIII) hydrochlorides.

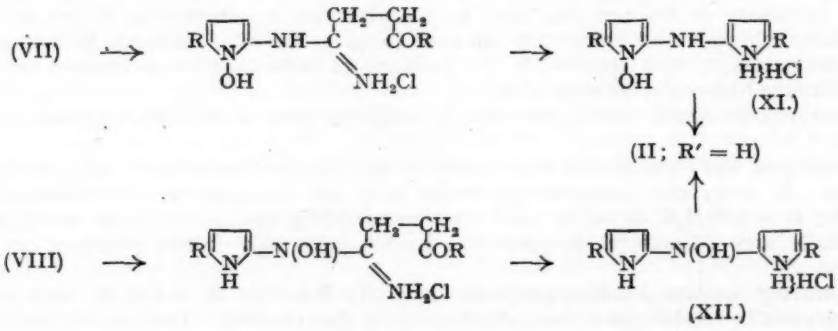


Oxime formation would appear to be the natural step, but it is significant that under no conditions could an oxime be isolated. It is well known (Nordmann, *Ber.*, 1884, **17**, 2747; Tiemann, *Ber.*, 1884, **17**, 126, 1685; 1886, **19**, 1475; 1889, **22**, 2391, 2942, etc.) that aliphatic nitriles, particularly those which are also readily hydrolysable, react with hydroxylamine or its salts to yield amidoximes. Thus the formation of (VI) is quite feasible, although under conditions used by Tiemann no product could be isolated.

There are no indications of the second-stage reaction, although it is known that γ-diketones will react with hydroxylamine to give substances analogous to (VII) (Knorr, *Annalen*, 1886, **236**, 296). It is also known that hydroxylamine will react with 1 : 3-dicyanopropane (Tiemann, *Ber.*, 1889, **22**, 2945; Biedermann, *ibid.*, p. 2967) or *o*-cyanobenzyl cyanide (Eichelbaum, *ibid.*, p. 2973) to give substances which are not the expected amidoximes, as they are insoluble in alkali. It is possible that cyclisation occurred, not as proposed by the above authors, but so as to give a dihydropyridine (IX) and an *iso*quinoline (X).



Such ring closures would then be analogous to the formation of (VIII). The third-stage reaction could proceed from either (VII) or (VIII) by addition of a further nitrile molecule followed by cyclisation and elimination of water to give the dye.



The precipitation of the dihydrochloride, which is more soluble in alcohol than the monohydrochloride, is difficult to explain, since it is unlikely that the dye is a stronger base than hydroxylamine.

Rogers (*loc. cit.*) found that 2-amino-3 : 5-diphenylpyrrole is readily oxidised to the azamethin, but such a mechanism for dye formation cannot be applied here, since no oxygen is present. He found also that 2-nitroso-3 : 5-diphenylpyrrole gives the azamethin on heating, and it is possible that (VIII) may also undergo self-condensation with the elimination of water and hydroxylamine.

All the dye salts gave similar blue solutions in organic solvents but differed in colour in the crystalline state. Striking differences, however, were shown in their behaviour towards concentrated sulphuric acid. The different colours given in hot and cold sulphuric acid and on precipitating the dye from the latter with water allow the identification of nearly all the dyes so far prepared (see Table I).

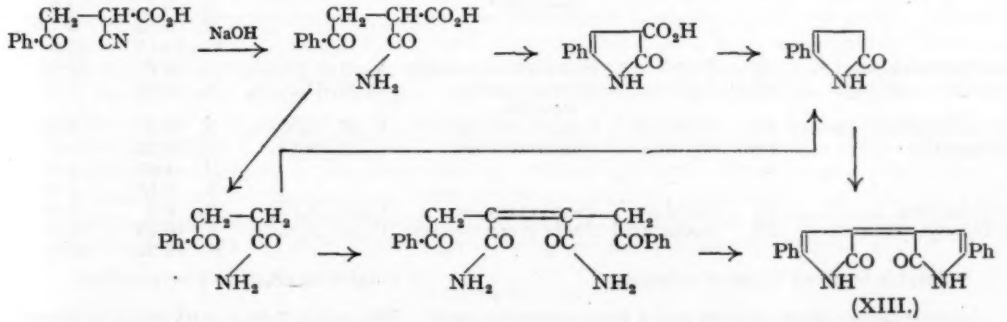
TABLE I.

II.	Cold H_2SO_4.	Addition to water.	Hot H_2SO_4.
R′ = H, R =			
Phenyl	Blue *	Magenta	Green ⟶ yellow
p-Tolyl	Green	Blue	Yellow ⟶ brown
p-Chlorophenyl	Blue	Blue	Green ⟶ yellow ⟶ brown
p-Bromophenyl.....	Blue	Blue	Yellow ⟶ red-yellow
p-Hydroxyphenyl.....	Orange	Magenta	Red
p-Methoxyphenyl	Orange	Blue-green	Red
m-Hydroxyphenyl	Purple	Magenta	Blue ⟶ yellow
m-Methoxyphenyl	Purple ⟶ blue	Magenta	Blue ⟶ yellow
3 : 4-Dimethoxyphenyl	Orange	Blue	Brown ⟶ red ⟶ brown
1-Naphthyl	Yellow ⟶ purple ⟶ blue	Blue	Blue ⟶ green ⟶ yellow
2-Naphthyl	" " "	Blue	" " "
2-Thienyl	Green	Blue	Red ⟶ yellow
R = R′ = Phenyl	Blue	Blue	Green ⟶ yellow

* Sulphate gave green solution.

As stated above, the dye obtained by Klobb from α-cyano-β-benzoylpropionic acid does not belong to the azamethin class. Apart from the analysis figures, the pale colour it gives in concentrated sulphuric acid is quite different from the deep colours given by (II). An alternative synthesis was found whilst experimenting with β-benzoylpropionamide with a view to the preparation of the dye observed on fusing the latter. Whereas alcoholic hydroxylamine salts did not give any dye on refluxing them with the amide, yet on replacing the alcohol by formamide and heating to 120° the latter reacted suddenly with the hydroxylamine hydrochloride (shown by separate experiment) with the evolution of ammonia, probably due to the formation of a hydroxamic acid (cf. Hoffmann, *Ber.*, 1889, **22**, 2854), and a secondary reaction caused the separation of a crystalline dye. The same dye was formed in very small amounts when the hydroxylamine hydrochloride was omitted. The dye had all the properties of Klobb's dye and analysis confirmed the identity.

Insufficient data have been collected on the dye to prove its structure, but it is suggested that it belongs to the *iso*indigotin class (cf. Wahl and Bagnard, *Bull. Soc. chim.*, 1909, **5**, 1039;



(XIII.)

1914, **15**, 329). Analysis agrees with its being *bis*-3-(2-*keto*-5-*phenyl*-2 : 3-*dihydropyrrolylidene*) (XIII). Its formation from (I; R = Ph, R′ = CO_2H) can be explained by hydrolysis by

alkali to the amide, followed by cyclisation, decarboxylation, and oxidation, or by decarboxylation, oxidation, and cyclisation as shown. The hydroxylamine salt–formamide process involves oxidation at one stage and it is not clear how this takes place.

The same dye is also readily formed from β-benzoylpropionamide, acetamide, and hydroxylamine hydrochloride, and the β-benzoylpropionamide may be replaced by the acid or ester. Lævulic acid did not give any dye under similar conditions.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss, Oxford; m. p.s are uncorrected.)

Bis-2-(5-phenylpyrrole)azamethin Dihydrochloride.—(*a*) β-Benzoylpropionitrile (15·9 g., 0·1 mol.), hydroxylamine hydrochloride (28 g., 0·4 mol.), and industrial methylated spirit (150 c.c.) were refluxed for 2 hours. After the semi-solid reaction mixture had cooled, the dye was collected and washed well with acetone. The yield of crude solid (16·2 g.) was 87·7%. The filtrate gave hydroxylamine hydrochloride (10·1 g.) on concentration. If boiling butanol is used as the solvent a magenta dye is also formed. It is readily removed, however, by washing with acetone. The *dye*, recrystallised from pyridine, formed purple needles of no definite m. p. (Found: C, 64·4; H, 5·05; N, 11·2; Cl, 20·2. $C_{20}H_{17}N_3Cl_2$ requires C, 64·85; H, 4·6; N, 11·35; Cl, 19·15%). The *monohydrochloride* was obtained as short needles from butanol or pyridine by pouring an alcoholic solution of the dihydrochloride into water (Found: C, 71·73; H, 4·8; N, 12·5; Cl, 10·5. $C_{20}H_{16}N_3Cl$ requires C, 71·95; H, 4·8; N, 12·6; Cl, 10·65%). The *sulphate*, obtained in low yield (37%) from the nitrile and hydroxylamine sulphate, was very insoluble in most organic solvents. It was obtained as small bronze needles (Found: N, 10·5. $C_{20}H_{17}O_4N_3S$ requires N, 10·65%).

(*b*) α-Cyano-β-benzoylpropionic acid hydrate (2·2 g., 0·01 mol.), hydroxylamine hydrochloride (1·4 g., 0·02 mol.), and industrial methylated spirit (10 c.c.) were refluxed for 90 minutes. The dye (1·0 g., 54%) was collected after cooling and recrystallised from pyridine. It formed alkali-insoluble purple needles (Found: C, 64·25; H, 5·0; N, 11·5%).

Bis-2-(3 : 5-diphenylpyrrole)azamethin.—(*a*) β-Benzoyl-α-phenylpropionitrile (4·7 g., 0·02 mol.), hydroxylamine hydrochloride (1·4 g., 0·02 mol.), and ethylene glycol (20 c.c.) were heated at 120° in an oil-bath for 2 hours. The dye separated as coppery crystals. These were collected when cold, and recrystallised from nitrobenzene forming short needles (0·3 g., 6·7%), m. p. 286° (Found: C, 84·9; H, 5·05; N, 9·5. Calc. for $C_{32}H_{23}N_3$: C, 85·5; H, 5·1; N, 9·4%). (*b*) With the same procedure as in (*a*) but using *n*-butyl alcohol (20 c.c.) as solvent and refluxing for 2 hours, the deep blue solution deposited the dye salt on chilling. The purple solid rapidly acquired a coppery sheen on standing in the atmosphere, owing to hydrolysis to the base (m. p. 286°) (1·2 g.; 26·7%). (*c*) The nitrile (4·7 g.), hydroxylamine hydrochloride (1·4 g.), and formamide (20 c.c.) were placed in an oil-bath at 120°. The temperature of the mixture rose to 90°, then with evolution of gas the temperature rose to 150° and the dye separated. It (0·8 g., 17·8%) was collected after dilution with alcohol, ground with alcohol, and washed with alcohol and water. It had m. p. 286° and was identical with the sample prepared according to (*a*).

Table II.

II; R′ = H, R =	Yield, %.	Solvent.	Crystal form.	Formula.	Analysis, %. Found.	Requires.
p-Tolyl	49·8	Acetic acid	Short bronze needles	$C_{22}H_{21}N_3Cl_2$	N, 10·4	10·55
p-Bromophenyl.....	41·5	Acetic acid	Short gold-green needles	$C_{20}H_{15}N_3Cl_2Br_2$	N, 7·5	7·95
p-Chlorophenyl	55	Acetic acid	Fine purple needles	$C_{20}H_{15}N_3Cl_4$	N, 9·5	9·6
p-Hydroxyphenyl *	—	Pyridine	Short green needles	$C_{20}H_{17}O_2N_3Cl_2$	C, 60·05	59·7
					H, 4·2	4·25
					N, 10·9	10·45
					Cl, 17·1	17·65
p-Methoxyphenyl ...	57	Pyridine	Short coppery needles	$C_{22}H_{21}O_2N_3Cl_2$	C, 60·65	61·4
					H, 5·3	4·9
					N, 9·55	9·75
					Cl, 16·15	16·5
m-Hydroxyphenyl †...	40	Pyridine	Short green needles	$C_{20}H_{17}O_2N_3Cl_2$	N, 10·55	10·45
m-Methoxyphenyl ...	46·5	Acetic acid	Short coppery needles	$C_{22}H_{21}O_2N_3Cl_2$	N, 9·45	9·75
3 : 4-Dimethoxyphenyl	52	Pyridine	Coppery needles	$C_{24}H_{25}O_4N_3Cl_2$	N, 8·5	8·55
1-Naphthyl	44·5	Pyridine	Purple threads	$C_{28}H_{21}N_3Cl_2$	C, 71·55	71·5
					H, 4·65	4·45
					N, 9·15	8·95
2-Naphthyl	37	Pyridine	Purple needles	$C_{28}H_{21}N_3Cl_2$	N, 9·2	8·95
2-Thienyl	23	Acetic acid	Short green needles	$C_{16}H_{13}N_3S_2Cl_2$	N, 10·45	11·0
					S, 16·35	16·8

* Soluble in alkali to green solution. † Soluble in alkali to blue solution.

Hydroxylamine Hydrochloride and β-Benzoylpropionamide.—The amide (7·08 g., 0·04 mol.), hydroxylamine hydrochloride (2·8 g., 0·04 mol.), and formamide (20 c.c.) were placed in an oil-bath at 120°. After a while the evolution of gas commenced and the *dye* separated rapidly. After 5 minutes the melt was diluted with alcohol, and the dye collected, and washed with alcohol until the washings were

colourless. It (0·5 g.) formed brassy, irregular plates from pyridine, in which it gives a magenta solution. It sublimed with some decomposition, giving red vapours. It was readily decolorised in pyridine solution with aqueous sodium dithionite (Found: C, 75·7; H, 4·6; N, 9·0. $C_{20}H_{14}O_2N_2$ requires C, 76·45; H, 4·45; N, 8·9%).

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226. *The Photochemical Polymerisation of Vinyl Acetate Vapour.*

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The kinetics of the polymerisation of vinyl acetate vapour under the influence of ultra-violet light of wave-lengths greater than 2500 A. have been investigated. Shorter wave-lengths cause decomposition of the molecule into products which inhibit the polymerisation. At high enough pressures the rate of polymerisation is proportional to the first power of the concentration of vinyl acetate and to the square root of intensity of the incident light. At pressures of about 20 mm. the rate falls off very rapidly and becomes immeasurably slow at lower pressures, *e.g.*, 15 mm. This phenomenon is apparently due to the fact that the photo-excited vinyl acetate molecule can lose its energy before another molecule of monomer can add on. This hypothesis is reinforced by the effect of other added gases. Quite small amounts of oxygen and of butadiene retard the reaction by terminating the growing chain. Amounts of inert gases like helium, argon, and hydrogen comparable with the amount of vinyl acetate also retard the polymerisation but these gases function, not by stopping growing chains, but by deactivating by collision the photo-excited vinyl acetate molecule.

THIS paper is a continuation of the work on the systematic examination of polymerisation reactions in the vapour phase. In practically every example of a vinyl derivative that readily polymerises in the vapour phase a number of unique observations have been made which have helped in elucidating the kinetics of such reactions. As will be seen below, the vinyl acetate reaction is no exception. As with methyl methacrylate and chloroprene, it happens that there are two distinct mechanisms whereby macromolecules are formed, and it turns out that it is easy to separate the two modes of polymerisation. Apart from these considerations, however, the polymerisation of vinyl acetate has been studied in the liquid phase, peroxide catalysts (Cuthbertson, Gee, and Rideal, *Proc. Roy. Soc.*, 1939, *A*, **170**, 300; Blaikie and Crozier, *Ind. Eng. Chem.*, 1936, **28**, 1155; Skirrow, *British Plastics*, 1939, **10**, 416, 507; Starkweather and Taylor, *J. Amer. Chem. Soc.*, 1930, **32**, 4708) and ultra-violet radiation (Taylor and Vernon, *ibid.*, 1931, **53**, 2527) being used. The results of these investigations are not sufficiently comprehensive to enable a decision to be made as to whether the mechanisms in the liquid phase are the same for photo- and peroxide-catalysed reactions: nor is it possible to say whether the mechanism in the gas phase is kinetically similar to that in the liquid phase.

It has been shown that in some dimerisations, *e.g.*, of *cyclo*pentadiene (Wassermann, *J.*, 1939, 362, 367, 371, 375), the bimolecular constants are the same in the liquid and in the vapour phase, and hence it seemed necessary to see whether in a suitable polymerisation process a similar identity of rates could be obtained. Vinyl acetate is one of the few monomers which polymerise equally well in both phases, and thus some information on this point might be obtained.

There is, however, another important reason for undertaking this work. In the liquid phase it is believed that polymerisation occurs by the free-radical mechanism, *i.e.*, the active polymer is a large free radical. Although it has been demonstrated that a free radical mechanism *can* occur in the liquid phase, it is by no means certain that every liquid-phase polymerisation proceeds by this mechanism. As will be shown, it is possible to characterise the free-radical polymerisation of vinyl acetate in the vapour phase. If therefore it can be shown that there is in fact a correlation in behaviour of vinyl acetate between the two phases, it may be possible to gain some more precise information about the behaviour in the liquid phase. The present paper is confined to the gas-phase polymerisation, and further communications will deal with the liquid-phase reaction. Polymerisation must be initiated by radiation, by excited mercury atoms, or by free radicals, since purely thermal polymerisation does not occur at all.

EXPERIMENTAL

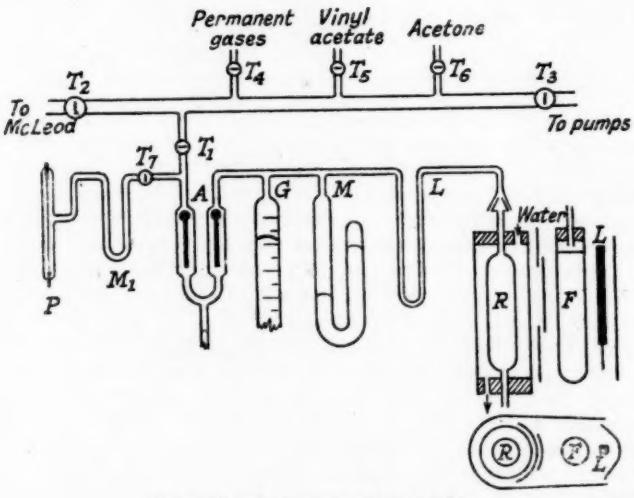
Apparatus.—The apparatus used calls for no special comment, the general arrangement being shown in Fig. 1. The silica reaction vessel was placed in a thermostat, and the polymerisation could be carried out at various temperatures up to 100° either under constant pressure of vapour, using a gas burette, or at constant volume, using a mercury manometer. Mercury cut-offs were employed to isolate the

reaction system to avoid trouble with greased joints. The apparatus was evacuated by a mercury diffusion pump. The sources of light were high- and low-pressure mercury lamps depending on the type of reaction being studied. Care was taken to ensure constancy of light output by controlling the voltage applied to the lamps. Experiment showed that, like other monomers, vinyl acetate is decomposed by the shortest wave-lengths emitted by the mercury lamp. Consequently it was necessary to screen off such radiation by acetic acid filters (30% aqueous solution). McLeod and Pirani gauges were used to measure the pressures of gases not condensable in liquid air.

Particular care was taken in the purification of vinyl acetate. This was originally obtained from Shawinigan Chemicals Ltd. and usually contained some acetaldehyde. The latter substance is a strong inhibitor of the liquid- and also the gas-phase polymerisation and hence its removal is essential. The monomer was first fractionally distilled twice at atmospheric pressure, only the 72—73° fraction being collected. The aldehyde is difficult to separate, and all fractions boiling below 72° were discarded. The nearly pure ester—which only gave a faint pink coloration with Schiff's reagent on standing for 5 minutes—was sealed into a tube on to the vacuum line of the apparatus. The ester was then frozen with liquid air and pumped out to 10^{-5} mm. It was melted and refrozen several times with evacuation between each cycle. Distillation was conducted in a vacuum, only the middle portion being used for experimental purposes.

"A.R." Acetone was used as a source of methyl radicals. It was freed from oxygen in a similar manner to the vinyl acetate. Oxygen came from potassium permanganate; hydrogen was purified by passing through palladium. Butadiene was taken from a cylinder and purified by vacuum distillation.

FIG. 1.



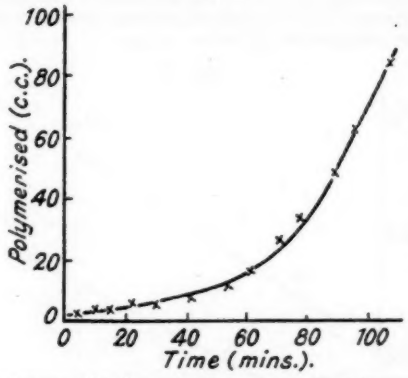
General arrangement of apparatus.

Direct Photo-reaction.—Several precautions have to be taken in measuring the velocity of polymerisation. Fig. 2 shows how the number of molecules polymerised increases with time of illumination, starting with a clean tube. There is a marked induction period, and gradually the rate attains a constant value. If illumination is prolonged, the rate begins to decrease again, but since this only occurs when very thick deposits of polymer are formed it is attributed to scattering and absorption of the effective radiation by the polymer. The long induction period is not due to the presence of gas-phase inhibitors, because a similar phenomenon is observed if successive separate portions of vinyl acetate are used. This points to an effect due to the reaction vessel itself. It is not due to the fact that the polymerisation really takes place in the deposited polymer. There are many reasons for supporting this contention. The customary mist of solid polymer is formed in the gas phase when the lamp is switched on, the polymerisation rate does not increase proportionally to the weight of polymer deposited, inert gases like helium, argon, and hydrogen inhibit the polymerisation, and the intensity exponent in the polymerisation does not tend to zero, as happens in the polymerisation of chloroprene where polymerisation does occur in the solid polymer. As will be shown later, there is little doubt that the induction period is due to the fact that the active polymer molecules are somehow destroyed when they collide with the clean silica walls, and that when these are covered by polymer there is more or less elastic reflection with a consequent lengthening of the chain until mutual destruction occurs in the gas phase. This suggestion is supported by covering the walls with a layer of Gelva 15—commercial polyvinyl acetate—whereby the induction period is diminished but curiously enough not completely eliminated. The other surprising fact is that walls need to be covered by a fairly thick layer of polymer. It might be expected that a monolayer of polymer would be sufficient. Assuming a degree of polymerisation of 100, a monolayer would correspond to a pressure decrease of 10^{-2} mm. whereas a very much greater decrease of pressure is required before the reaction rate is constant. Owing to the necessity for depositing polymer there is a measurable absorption of the monomer by the polymer, and as this amount of polymer increases so the amount of sorbed monomer increases. Corrections are

made for the total observed consumption of monomer to give the true photo-rate. In order to cut down corrections of this kind to a minimum, the method of bracketing must be employed, and tubes are used for a relatively small number of runs just after conditions have become relatively steady. Experiments show there is no measurable induction period and that there is no long-continued reaction in the dark, as occurs with methyl methacrylate. This is in accord with the present experience with molecules of the type $CH_2{:}CHX$. If a heavily coated tube is being used there is sometimes an apparent induction period or even a pressure increase, due apparently to some desorption of monomer from the polymer when the light is switched on.

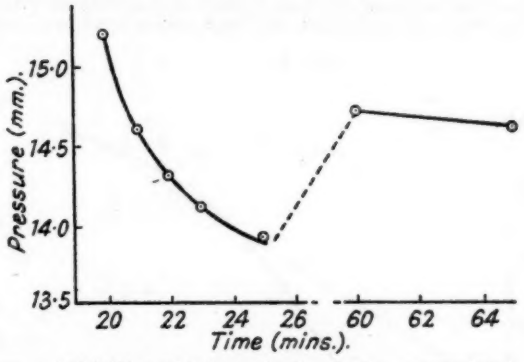
General Kinetics.—Decomposition. As has already been mentioned, unfiltered light from the mercury lamp leads to decomposition of the vinyl acetate, one of the products of decomposition being non-condensable in liquid air. This gas could only be hydrogen, carbon monoxide, or methane. A Pirani gauge was consequently calibrated by using carbon monoxide and hydrogen. The gas from vinyl acetate gave a calibration curve coinciding exactly with that for carbon monoxide. The calibration curve for methane lies very close to that for carbon monoxide and therefore it is difficult to say whether

FIG. 2.



Course of polymerisation at constant pressure starting with a clean tube.

FIG. 3.



Inhibition of polymerisation by the accumulated products of decomposition of vinyl acetate.

the gas is one or the other. The important point of this decomposition is that the products are strong inhibitors for the photo-polymerisation. This behaviour is shown most clearly by the following kind of experiment. Vinyl acetate is illuminated at constant volume for a given period and the rate measured. After this, the pressure is increased to the initial value and the run continued. As Fig. 3 shows, there is a very marked diminution in rate as a result of the accumulation of the products of decomposition. The acetic acid filter completely eliminates this decomposition, and hence it would appear that it has nothing to do with the polymerisation reaction. Another indication in support of this suggestion is that decomposition occurs just as readily below the critical pressure at which vinyl acetate ceases to polymerise. These observations are completely in accord with experience with methyl methacrylate and methyl acrylate. Short-wave radiation, instead of leading to activation and eventual starting of polymerisation, simply results in disruption of the molecule into products incapable of starting polymerisation.

Effect of pressure. The constant-pressure technique being used, the variation of rate with pressure was investigated, due regard being paid to corrections owing to disappearance of monomer by absorption by the polymer. A typical run is shown in Table I, the bracketing pressure being 42·1 mm. Similar

TABLE I.

Direct photo-polymerisation; temp. 20°; *high-pressure* Hg *lamp.*

Pressure (mm.).	Observed rate (in c.c./min.) at 42·1 mm. pressure.	Dark " rate " (c.c./min.).	Net polymerisation rate (c.c./min.).
42·1	25·6	0·8	24·8
42·1	27·3	1·9	25·4
37·5	22·1	—	22·1
23·9	3·56	—	3·56
42·1	26·5	1·4	25·1
48·4	31·6	2·0	29·6
55·6	40·4	1·6	38·8
42·1	30·4	2·0	28·4

series of runs were made over other ranges of pressure, the maximum being fixed at about 60 mm., the saturation vapour pressure of vinyl acetate. Rates relative to that at 42·1 mm. are plotted as a function of pressure in Fig. 4. The most striking feature of this plot is the appearance of a limiting pressure below which the reaction rate is immeasurably slow. At high enough pressures the rate is approximately proportional to the first power of the pressure, whereas in the intermediate region 20—40 mm.

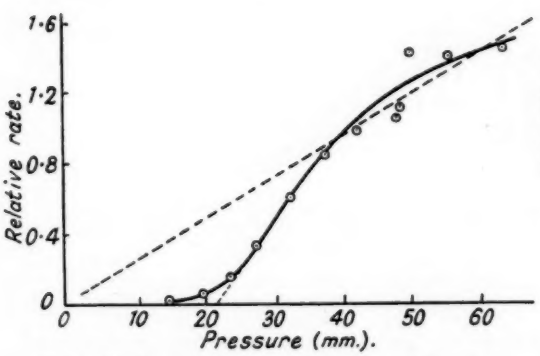
the rate = const. $(p - p_0)$, where p_0 may be defined as a critical pressure of about 21 mm. This limit has nothing to do with inhibition by decomposition products, for if the vapour is illuminated at, say, 20 mm. for a considerable period and the pressure is then raised to say 30 mm., polymerisation proceeds normally. Similarly, if polymerisation is occurring at 30 mm. and the pressure is reduced to 20 mm. polymerisation immediately ceases. To show this more clearly prolonged illumination with use of the acetic acid filter gave the following results:

Vinyl acetate pressure (mm.).	Time of illumination (mins.).	C.c. of vapour polymerised.	Pressure of products of decomposition (mm.) (non-condensable in liquid air).
12·9	120	—	$4·0 \times 10^{-2}$
15·0	100	8·0	$3·5 \times 10^{-2}$

It will be seen that a reduction in pressure of only 2 mm. reduces the very small rate of polymerisation at 0·08 c.c./min. to an immeasurable value, yet the decomposition is hardly affected. Likewise there is no photo-decomposition of the polymer and hence this could not be the cause of the appearance of the limit.

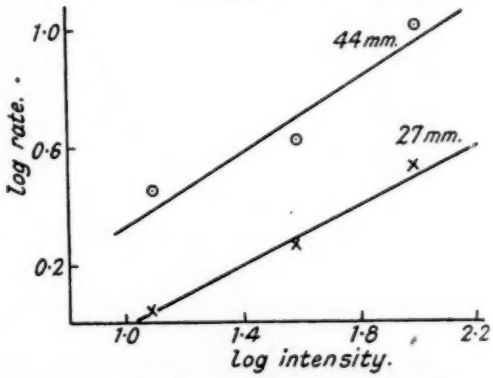
That the phenomenon has something to do with the initiation process is shown by the fact that if a low-pressure mercury lamp is used, and presumably therefore excited mercury atoms are responsible for starting polymerisation, the limit is displaced to a lower pressure at 12 mm.

FIG. 4.



Rate of polymerisation as a function of pressure.

FIG. 5.



Variation of rate with intensity of incident illumination.

Intensity exponent. The variation of polymerisation rate with intensity of light gives useful information in regard to the order of the process in which the active polymer molecule is destroyed. It is particularly important to measure this exponent in view of the gradual increase of rate with the amount of polymer deposited and the existence of the critical limit. The intensity was decreased by using perforated screens which had been previously calibrated by a photoelectric cell. Runs were made at high pressure where the rate is proportional to pressure and at as low pressure as possible to see whether in the vicinity of the limit there was any change in the mechanism of the termination process. A logarithmic plot of the results is given in Fig. 5. The slope of these curves is 0·60 and 0·55 for 44 and 27 mm., respectively, which is a sure indication that polymerisation stops when two active polymers mutually destroy each other. This again furnishes additional proof that the appearance of the limit has nothing to do with the termination process.

The same set-up being used, the value of the critical limit was measured for an intensity only one-eighth of that used in the measurements given on p. 1203. The following results give a limit on extrapolation of 21 mm. Thus, in spite of a diminution in rate of starting of polymerisation by a factor of 8 and an increase in chain length by a factor of 3, the limit is unaffected.

Vinyl acetate press. (mm.)	19·1	25·3	38·2	46·0
Rate (c.c./min.)	0·25	1·05	4·76	5·85

Effect of temperature. Rather a complicated procedure had to be adopted in these experiments, for at each temperature a series of runs at different pressure had to be made in virtue of the existence of the critical limit, since it was essential to find whether the limit itself was dependent on temperature. To ensure that the condition of the tube was as nearly similar as possible during these experiments, before and after each series of runs at elevated temperature standard runs were made at 20° and at 42 mm. pressure. It was not possible to go to temperatures greater than 100° since decomposition of the polymer led to complications and the rate fell off very quickly above this temperature. The results are summarised in Fig. 6, where the relative rates are plotted against pressure for a series of temperatures. At pressures above 30 mm. it will be seen that the rate decreases with increasing temperature. This phenomenon, although observed with methyl acrylate and methyl vinyl ketone, might be due to the intervention of some inhibitor or to a change in the nature of the termination reaction. Using a pressure of 60 mm. at 66°, a measurement of the variation of rate with intensity gave the following results:

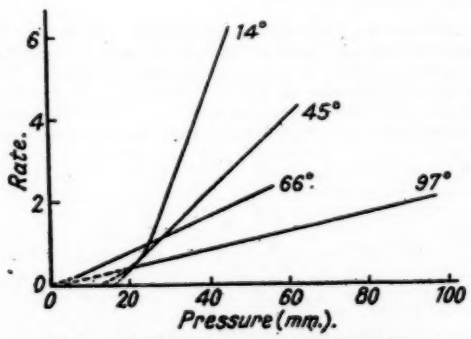
Intensity	1·00	0·384	0·125
Rate (mm./min.)	0·63	0·38	0·185

This corresponds to an exponent of 0·60, in agreement with the results at 20°. Hence, mutual termination of chains still operates at elevated temperatures. At each temperature the variation of rate with pressure is represented by the equation Rate $= k(p - p_0)$, except in the neighbourhood of the limit, defined for the sake of convenience by p_0 in this equation. The following results show how the value of p_0 varies with temperature:

Temp.	14·0°	46°	66°	97·0°
p_0 (mm.)	21·0	16·0	6·0	5·0

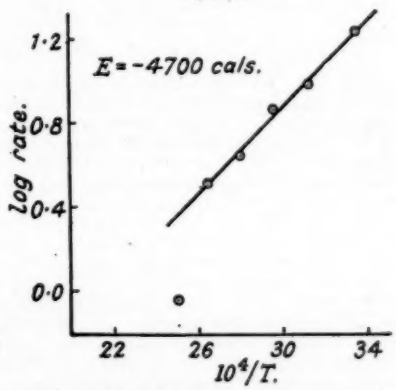
Hence, at above 100° the polymerisation pursues a normal course in which $R = \text{const.}\ (I_{abs.})^{\frac{1}{2}}\ (M)$, which are kinetics compatible with the idea that all the light is absorbed and that mutual termination of the polymer chain occurs almost exclusively (Gee and Melville, *Trans. Faraday Soc.*, 1944, **40**, 240). Below 30° an inversion of the temperature coefficient occurs and the rate increases with increase in temperature. This kind of anomalous behaviour is, however, primarily due to the intervention of some reaction responsible for the appearance of the limit—a reaction which itself possesses a temperature coefficient. In absence of this complicating phenomenon, namely, at as high pressure as can be obtained, there is no doubt that the polymerisation rate decreases with increasing temperature. The temperature coefficient was therefore measured for a pressure of 50 mm. and the log Rate–$1/T$ plot is shown in Fig. 7. The slope corresponds to an apparent energy of activation of −4700 cals. The point at 128° is obviously

FIG. 6.



Rates of polymerisation as a function of pressure at a series of temperatures.

FIG. 7.



Temperature coefficient of the rate of polymerisation at 50 mm. pressure of vinyl acetate (T = ° K.).

so far off the straight line as to indicate a complete change in mechanism which has not been further investigated. It being assumed that the energy of activation for the initiation process is negligible, this means that there is an energy of activation for the termination process and that it exceeds that of the propagation reactions for with mutual termination $E_{app.} = E_{prop.} - \frac{1}{2}E_{term.}$, where $E_{prop.}$ and $E_{term.}$ are the energies for propagation and termination, respectively. Only in the case of methyl acrylate has there been made a *minimum* value for $E_{prop.}$ and this amounts to 4000 cals. (Melville, *Proc. Roy. Soc.*, 1938, *A*, **167**, 99). Even if it is supposed that $E_{prop.}$ in the vinyl acetate reaction is 5000 cals., $E_{term.}$ amounts to about 20,000—a very high value indeed. In fact, considering the small concentration of active polymers, it would appear that the termination reaction would hardly ever occur in the gas phase at room temperature. There is here a peculiarity in a number of photo-gas-phase polymerisations which is kinetically not easily understandable. Yet with methyl acrylate if a strong inhibitor, *e.g.*, oxygen or butadiene, is added to change completely the nature of the termination process the apparent temperature coefficient becomes positive, since a termination process normally requiring activation energy is replaced by one in which the energy of activation is practically zero. The phenomenon is not confined to gas-phase polymerisation, for in some liquid-phase polymerisations the chain length of the polymers decreases with increasing temperature, possibly owing to the energy of activation for termination exceeding that for propagation.

The critical limit. Before attempting to discuss the abnormal pressure dependence of this polymerisation the main kinetic features may be summarised as follows: (*a*) The rapid falling off in rate at low pressures and temperatures—the reaction being apparently normal at high temperatures and pressures. (*b*) Dependence of the "limit" on temperature. (*c*) Independence of limit on intensity and state of the tube, *i.e.*, whether covered or not. (*d*) Termination mechanism of polymerisation not altered in the low-pressure, low-temperature region. (*e*) Limit apparently affected by *mode* of initiation.

The limit appears to have no connection with the explosion limit in other chain reactions, for the rate above the limit is in no sense indefinitely fast, the reaction being under complete control. The best proof of this suggestion is that the intensity exponent never falls below 0·5 whereas in an incipient explosion, *e.g.*, in the H_2–N_2O–O_2 system sensitised by hydrogen atoms, the exponent may fall below the normal value of 0·5 when the reaction gets out of hand (Melville, *Proc. Roy. Soc.*, 1934, *A*, **146**, 737).

It would appear to be necessary to introduce some mechanism at low pressures which leads to a diminution in velocity rather than introduce some phenomenon which leads to an abnormal increase

in rate at high pressures as in gaseous explosions or in the polymerisation of methyl vinyl ketone (Jones and Melville, *ibid.*, 1946, *A*, **187**, 19). All the above evidence indicates that neither termination nor propagation factors are affected and that therefore the phenomenon has something to do with the initiation process. The shift of the limit by changing from direct to sensitised initiation and the non-existence of the limit in the radical-sensitised reaction are additional certain pointers to this conclusion. It is probable that the primary photochemical efficiency is not high, *i.e.*, some of the energy absorbed by the vinyl acetate molecule is lost before another molecule of monomer can react with it. Thus we may have two competing processes:

$$\begin{aligned} M + h\nu &= M^* \quad \ldots\ldots f(I) \\ M^* + M &= P_2 \quad \ldots\ldots k_{p_1} \\ M^* &= M \quad \ldots\ldots k_s \end{aligned}$$

As the pressure is reduced, a greater proportion of the M* molecules lose their energy by some kind of a process not involving a collision with a monomer molecule. Mutual termination being assumed, then

$$d[M^*]/dt = f(I) - k_s[M^*] - k_{p_1}[M^*][M] = 0$$

and in general

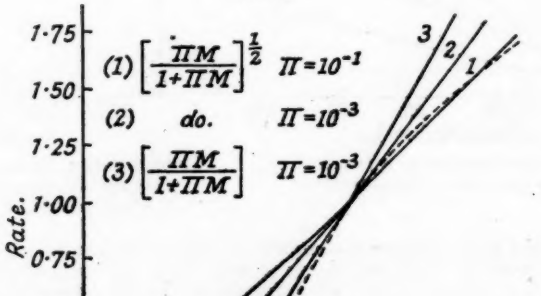
$$d[P_n]/dt = k_{p_{n-1}}[P_{n-1}][M] - k_{p_n}[P_n][M] - k_{t_n}[P_n]\Sigma k_{t_n}[P_n] = 0$$

Solving these equations in the usual way, we have

$$\begin{aligned} -d[M]/dt &= [M]\{f(I)\}^{\frac{1}{2}}\delta^{-1}\{k_{p_1}[M]/[k_s + k_{p_1}(M)]\}^{\frac{1}{2}} \\ &= [M]f(I)^{\frac{1}{2}}\delta^{-1}\{\pi[M]/[1 + \pi(M)]\}^{\frac{1}{2}} \end{aligned}$$

where $\pi = k_{p_1}/k_s$. At high values of [M], this gives linear dependence of rate on [M], but at low pressure the rate only varies as $[M]^{3/2}$ and would obviously not fall off quickly enough to be in accordance with experimental results. This is best shown by computing a value of π from experimental results. Assuming that the reaction is normal at 50 mm. and taking the rate at 24 mm., we have in the region of abnormality $R = 0{\cdot}16$, $\pi = 3{\cdot}0 \times 10^{-3}$ with [M] in mm. At 20 mm. $\pi = 0{\cdot}6 \times 10^{-3}$. Hence, taking a mean value of 10^{-3} and plotting the rate–pressure curve in Fig. 8 such that at one point, namely,

FIG. 8.



Relationship between theoretical and experimental curves, for the variation of rate with pressure.

40 mm., it is adjusted to coincide with the broken experimental curve, it will be seen that although the shape is approximately right the agreement both at low and at high pressures is such that the theory is not good enough to account for the observations. A better approximation may be obtained if it is assumed that not only the activated monomer but also the dimer may spontaneously lose its energy. Thus the scheme would be:

$$\begin{aligned} M + h\nu &= M^* \quad \ldots\ldots f(I) \\ M^* &= M \quad \ldots\ldots k_{s_1} \\ M^* + M &= M_2^* \quad \ldots\ldots k_{p_1} \\ M_2^* &= M_2 \quad \ldots\ldots k_{s_2} \\ M_2^* + M &= P_3 \quad \ldots\ldots k_{p_2} \end{aligned}$$

This leads to an expression

$$-\frac{d[M]}{dt} = [M]\delta^{-1}f(I)^{\frac{1}{2}}\left[\frac{k_{p_1}[M]}{k_{s_1} + k_{p_1}[M]}\right]^{\frac{1}{2}}\left[\frac{k_{p_2}[M]}{k_{s_2} + k_{p_2}[M]}\right]^{\frac{1}{2}}$$

If $k_{p_1}/k_{s_1} = k_{p_2}/k_{s_2} = \pi$, which is a reasonable assumption, this simplifies to

$$-\frac{d[M]}{dt} = [M]\delta^{-\frac{1}{2}}f(I)^{\frac{1}{2}}\left(\frac{\pi[M]}{1+\pi[M]}\right)$$

and as will be seen from Fig. 8 gives a plot agreeing more closely with the results below 40 mm., although the high-pressure agreement is inferior. The intervention of this kind of deactivation process might be extended to higher active polymers, but it is evident that the process cannot extend indefinitely for it would constitute another way in which the active polymers are destroyed, whereas the intensity exponent clearly indicates mutual destruction of the active polymers. Although the above theory does not quantitatively account for the shape of the R–p curve, it is in accordance with the observations made in connection with the position of the so-called limit, namely, independence of intensity and of the state of the vessel. Since the limit depends on temperature, this means that π increases with increasing temperature. This is entirely in accordance with expectation; k_{s_1}, k_{s_2} are unlikely to be affected by temperature, since spontaneous loss of large amounts of energy is unlikely to be influenced by relatively small changes in energy; k_{p_2}, on the other hand, is a propagation coefficient and will certainly increase with increasing temperature. The theory is not good enough to enable π or some similar parameter to be accurately computed, but an approximate estimate may be made in the following manner. Suppose there is no appreciable spontaneous deactivation at 40 mm. and the pressure $p_{\frac{1}{2}}$ is found from Fig. 8 at which the rate is half what it would have been in absence of this effect; then at this pressure the probabilities of propagation and deactivation are equal, and if $p_{\frac{1}{2}}'$ and $p_{\frac{1}{2}}''$ are the pressures at two temperatures, the energy of activation of the propagation reaction will be given by

$$E_p = 4{\cdot}57 \log_{10}\frac{p_{\frac{1}{2}}'}{p_{\frac{1}{2}}''}\frac{T_1T_2}{(T_1 - T_2)}$$

where T_1 and T_2 are the corresponding temperatures. For 14°, $p_{\frac{1}{2}}' = 28$ mm. and at 45° $p_{\frac{1}{2}}'' = 22$ mm.; hence $E_p = 1400$ cals.

Nature of the Photopolymer.—The polymer deposited as a result of the photochemical reaction is insoluble—a drawback which prevents a direct measurement of the chain length of the reaction. In view of the small number of cross-links needed to render a polymer insoluble, it is not unreasonable to suppose that the reaction responsible for branching and the type of links involved in the process may be entirely different from those constituting the main bulk of the polymer. The polymer was therefore formed under carefully controlled conditions by running the experiment at a constant pressure of 30 mm. and 15° until about 0·6 g. of polymer was deposited. The polymer was then washed out of the reaction vessel with acetone, in which it swelled but did not dissolve. The resulting material was suspended in dry methyl alcohol and treated with methyl-alcoholic potassium hydroxide. The white suspension so obtained was poured into water, in which it was completely soluble. Hence, conversion of the polyvinyl acetate into polyvinyl alcohol resulted in a breakdown of the three-dimensional polymer, which points to the fact that a hydrolysable link is responsible for joining the primary chains of the polymer together.

Inhibition.—A study of the effect of inhibitors on a chain reaction throws much light on the mechanism of the reaction. As will be shown, this is particularly true with vinyl acetate where a variety of inhibitory mechanisms may operate. Oxygen and butadiene are both effective inhibitors but, surprisingly enough, chemically inert gases like argon, helium, and hydrogen also function as inhibitors.

Oxygen. According to the theory of polymerisation (Gee and Melville, *Trans. Faraday Soc.*, 1944, **40**, 240) the expression for the rate of a completely inhibited reaction is

$$-d[M]/dt = [M]f(I)/\beta[O_2]$$

where $\beta = k_d/k_p$, k_d being the velocity coefficient for the interaction of inhibitor with active polymer. In order to get reliable results, the bracketing technique was employed for these experiments, *i.e.*, every run with the inhibitor present was preceded and followed by a run with pure vinyl acetate. With a pressure of 30 mm., the results of a series of runs are shown in Fig. 9, where reciprocal rate is plotted against oxygen pressure. In accordance with the theory, a straight line may be drawn through the points. Another result of inhibition of a reaction which is normally terminated by mutual destruction of the active polymers is that the intensity exponent should simultaneously increase from 0·5 to a value approaching 1·0 depending on the extent of the inhibition. A typical set of runs is given in Table II, the bracketing technique being employed and decrease of pressure being used for the measurement of rate.

TABLE II.

Vinyl acetate pressure, 31 *mm. Temp.* 20°.

Oxygen (mm.)	0	1·2	1·2	1·2	0
Intensity	1·00	1·00	0·125	1·00	1·00
Time (mins.) for pressure to fall 1 mm.	1·8	5·0	23·0	5·0	2·1

Intensity exponent = 0·74.

This increase of exponent to 0·74 clearly shows that inhibition is termination of growth of the polymer by the interaction of oxygen with it.

As will be shown in the following paper, it is possible to study the kinetics of the free-radical polymerisation below the critical limit, and thus in absence of the direct photopolymerisation. Table III shows that oxygen has no effect on the reaction initiated by methyl radicals and only a comparatively small effect on that initiated by hydrogen atoms, and this in spite of the fact that the rates of polymerisation are approximately the same as those in Table II. The fact that oxygen slightly inhibits the

TABLE III.

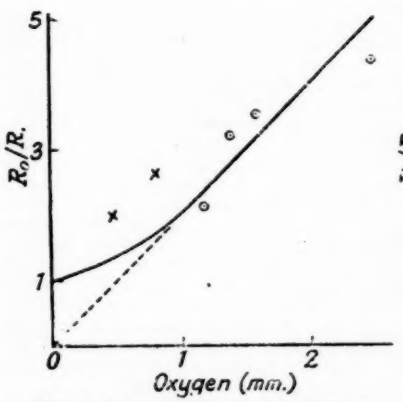
Effect of oxygen on free-radical-sensitised reaction at 20°.

Vinyl acetate press. (mm.).	Acetone (mm.).	Oxygen (mm.).	Rate (mm./min.).	Vinyl acetate.	Hydrogen.	Oxygen.	Rate.
Methyl radical reaction.				Hydrogen atom reaction.			
17·3	45	0·1	0·217	14·3	43	—	0·45
17·8	48	—	0·207	15·5	46	2·3	0·30
16·7	53	3·2	0·240	14·7	48	—	0·42
17·1	57	—	0·241				

hydrogen-atom reaction is quite possibly due to direct interaction of hydrogen atoms and oxygen molecules. The important point is that oxygen clearly discriminates between the two kinds of reaction.

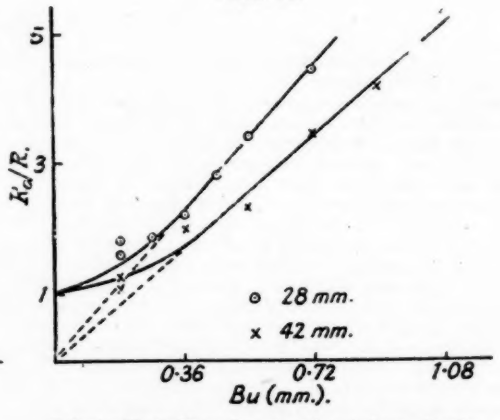
Butadiene. Butadiene is a more powerful inhibitor than oxygen and hence smaller pressures of the gas are needed. A gas pipette method was therefore adopted for introducing butadiene into the reaction system. The results at two vinyl acetate pressures are plotted in Fig. 10, in which the relative reciprocal rate is graphed against butadiene pressure. In these experiments bracketing methods were employed at all stages. Since in this case there is always the possibility of butadiene actually inter-polymerising with the vinyl acetate, with a resultant diminution in velocity, instead of acting as does oxygen, the variation of rate with intensity was measured. In the former case the square-root dependence would

FIG. 9.



Effect of oxygen in retarding polymerisation.

FIG. 10.



Effect of butadiene in retarding polymerisation, at 28 and 42 mm. of vinyl acetate.

still hold, while in the latter a linear dependence should be observed. The detailed results need not be given here except the following summary:

R_0/R.	$R_{1\cdot00}/R_{0\cdot125}$.	Exponent.	R_0/R.	$R_{1\cdot00}/R_{0\cdot125}$.	Exponent.	R_0/R.	$R_{1\cdot00}/R_{0\cdot125}$.	Exponent.
1·0	3·4	0·60	2·8	5·3	0·80	4·2	7·9	0·99

As the degree of inhibition (R_0/R) increases, the ratio of rates ($R_{1\cdot00}/R_{0\cdot125}$) at a fixed ratio of intensities likewise increases, corresponding to a general increase in intensity exponent. Additional confirmation is obtained in the following typical experiment with a vinyl acetate pressure of 33 mm. and butadiene 0·1 mm.: R_0/R at maximum intensity was 2·8, increasing to 3·9 at 0·125 of the maximum intensity. Thus, by reducing intensity and increasing thereby the chain length, the degree of inhibition is correspondingly increased. All these experiments conclusively show that when butadiene reacts with vinyl acetate active polymer it adds on and then the reaction stops. Normal molecules of vinyl acetate cannot react with a butadiene end of the polyvinyl acetate.

There is, however, one discrepancy. For the normal and the inhibited reaction we have respectively for the two rate equations:

$$-\mathrm{d[M]}/\mathrm{d}t = R_0 = \mathrm{[M]f}(I)^{\frac{1}{2}}/\delta \text{ and } R = \mathrm{[M]f}(I)/\beta\mathrm{(X)}$$

Hence

$$R_0/R = \beta\mathrm{[X]}/\delta\mathrm{f}(I)^{\frac{1}{2}}$$

As seen above, this relationship is followed in regard to butadiene concentration and light intensity. It will be noted that the value of R_0/R is independent of R_0 and, more important, independent of [M], yet in Fig. 10 the plots for two values of [M] are not coincident. One possibility is that $\mathrm{f}(I)^{\frac{1}{2}}$ depends on [M] because of incomplete absorption of radiation. The slope of the R_0/R or [X] curve would be less for higher values of [M], which is in qualitative agreement with observation. The maximum change of slope in this case would be 1·2 : 1 whereas the observed value is 1·25 : 1. The linear dependence of R on [M] at high enough temperatures would preclude this explanation. At lower pressures such as

28 mm., however, the vinyl acetate reaction begins to deviate quite markedly from normal behaviour. In order to get an expression for the reaction rate as a function of inhibitor concentration, an additional term, *viz.*, $k_{d_n}[P_n][X]$, is introduced into the differential equations defining $[\cdot P_n]$. This gives by the usual method

$$-\mathrm{d[M]/d}t = [\mathrm{M}]\{\mathrm{f}(I) - k_{s_1}[\mathrm{P_1}^*]\}/\beta[\mathrm{X}]$$

But

$$[\mathrm{P_1}^*] = \mathrm{f}(I)/\{k_{s_1} + k_p[\mathrm{M}] + k_{d_1}[\mathrm{X}]\}$$

Therefore

$$-\mathrm{d[M]/d}t = \frac{[\mathrm{M}]\mathrm{f}(I)}{[\mathrm{X}]\beta}\left\{\frac{k_{p_2}[\mathrm{M}] + k_{x_1}[\mathrm{X}]}{k_{s_1} + k_x[\mathrm{X}] + k_{p_2}[\mathrm{M}]}\right\}$$

Using the expression already obtained for the rate of reaction in absence of inhibitor, we have

$$R_0/R = \frac{\beta[\mathrm{X}]}{\delta \mathrm{f}(I)^{\frac{1}{2}}}\left\{\frac{k_{p_2}'[\mathrm{M}]}{k_{p_2}[\mathrm{M}] + k_{s_1}}\right\}^{\frac{1}{2}}\left\{\frac{k_{s_1} + k_{p_2}[\mathrm{M}] + k_{d_1}[\mathrm{X}]}{k_{d_1}[\mathrm{X}] + k_{p_2}[\mathrm{M}]}\right\}$$

It has already been shown that $k_p/k_s \approx 10^{-3}$, hence $k_s \gg k_p[\mathrm{M}]$ or $k_x[\mathrm{X}]$ and

$$R_0/R = \frac{\beta k_s^{\frac{1}{2}}}{\delta \mathrm{f}(I)^{\frac{1}{2}}} \cdot \frac{[\mathrm{M}]^{\frac{1}{2}}[\mathrm{X}]}{[\mathrm{M}] + \beta^{-1}[\mathrm{X}]}$$

Thus if $[\mathrm{M}] \approx \beta^{-1}[\mathrm{X}]$, decreasing values of [M] will increase the slope of the R_0/R–[X] curve.

Effect of Inert Gases.—Experiments with polymer-coated tubes seemed to indicate the existence of wall deactivation of the active polymer with clean or partly coated tubes. Thus it might be expected that the decrease in diffusion coefficient effected by the addition of inert gas might accelerate the polymerisation rate. When the experiment was done, precisely the opposite effect was obtained, a marked inhibition being observed. At first sight, this phenonenon is difficult to explain, since it is inconceivable that gases like argon, helium, and hydrogen could effect any chemical change in the active polymer that would lead to deactivation. As will be shown, inhibition does not occur by the termination of growth of the chains but is due to deactivation of excited molecules in the very early stages of polymerisation. This effect, indeed, is not then so unexpected in view of the abnormal pressure dependence of reaction and, in fact, provides further support for the hypothesis advanced to explain the occurrence of an apparent critical limiting pressure. Thus we have the curious phenomenon that inhibition by inert gases leads to an *increase* in chain length of the polymer and not a decrease as is usually the case.

The argon was obtained from a cylinder of the gas and was oxygen free. The helium was purified from more condensable gases by repeated treatment with active charcoal.

The results with argon for a series of vinyl acetate pressures are shown in Fig. 11. R_0/R and also $(R_0/R)^2$ are plotted against argon pressure. It is difficult to say which relationship is the better approximation, but one observation is important. Unlike those for oxygen and butadiene, these lines do not go through the origin but make an intercept of unity in the R_0/R axis. This at once shows that a different kind of inhibition comes into operation apart altogether from the fact that very much higher pressures are needed for inhibition to be observed. This is completely confirmed by measuring the intensity exponent. With a vinyl acetate pressure of 40 mm. and an argon pressure of 67 mm., $R_0/R = 2$, the intensity exponent is 0·60, the same value being obtained in the uninhibited reaction. This evidence certainly points to inhibition occurring in the initial stages of the reaction. Since the theory of the critical limit postulates the existence of an excited monomer which does not necessarily add on another molecule of monomer but may spontaneously lose its energy, probably by some internal rearrangement (it is hardly likely that chemical decomposition occurs, since it was earlier shown that decomposition seems to be an independent process brought about by short wave-lengths), it is natural to suppose that deactivation can also be brought about by collision with another molecule which facilitates this rearrangement or removes some of the energy from the excited molecule. In the expression for the value of $[\mathrm{P_1}]$ another term has therefore to be added and the appropriate equation becomes

$$\mathrm{d[P_1]/d}t = \mathrm{f}(I) - k_{p_1}[\mathrm{P_1}^*][\mathrm{M}] - k_{s_1}[\mathrm{P_1}^*] - k_{A_1}[\mathrm{P_1}^*][\mathrm{A}] = 0$$

Hence

$$R_0 = [\mathrm{M}]\delta^{-1}\mathrm{f}(I)^{\frac{1}{2}}\{k_{p_1}[\mathrm{M}]/k_{s_1} + k_{p_1}[\mathrm{M}])\}^{\frac{1}{2}}$$

and

$$R = [\mathrm{M}]\delta^{-1}\mathrm{f}(I)^{\frac{1}{2}}\{k_{p_1}[\mathrm{M}]/(k_{p_1}[\mathrm{M}] + k_{\ 1} + k_{A_1}[\mathrm{A}]\}^{\frac{1}{2}}$$

Therefore

$$R_0/R = \left\{1 + \frac{k_A[\mathrm{A}]}{k_{s_1} + k_{p_1}[\mathrm{M}]}\right\}^{\frac{1}{2}}$$

If argon deactivation is extended to $\mathrm{P_2}^*$ and we assume that $k_{p_1} : k_{s_1} : k_{A_1} = k_{p_2} : k_{s_2} : k_{A_2}$, then

$$R_0/R = 1 + k_A[\mathrm{A}]/(k_{s_1} + k_{p_1}[\mathrm{M}]$$

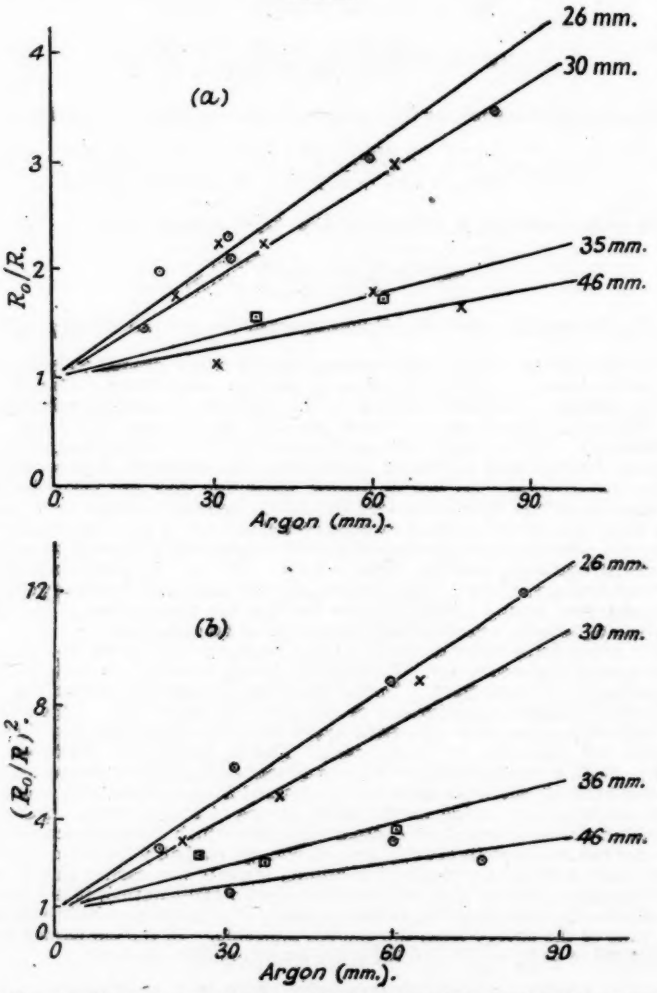
Rearranging these expressions, we have

$$\{(R_0/R)^2 - 1\}^{-1} = \frac{k_s}{k_A[\mathrm{A}]} + \frac{k_p}{k_A[\mathrm{A}]}[\mathrm{M}]$$

$$(R_0/R)^2 - 1 = k_A[\mathrm{A}]/k_{\ } + k_{p_1}[\mathrm{M}] \text{ and } R_0/R - 1 = k_A[\mathrm{A}]/\{k_{s_1} + k_{p_1}[\mathrm{M}]\}$$

Fig. 11 shows that a linear plot or R_0/R against argon pressure is obtained, and that the slopes of the lines are inversely proportional to the pressure of vinyl acetate. The intercept on the ordinate does not vary with argon pressure. This is not unexpected in view of the close approach to the critical limit when such relationships will break down. Experimentally it is difficult to decide between these two mechanisms.

FIG. 11.



Effect of argon in retarding the rate of polymerisation at various vinyl acetate pressures indicated. Figs. 11a *and* 11b *show alternative ways of plotting the results.*

Helium and hydrogen function in a similar manner, the intensity exponent not being affected when inhibition takes place. According to the above theory, the relative efficiencies of these gases can be obtained by plotting $(R_0/R)^2$ against the pressure of inert gas for a given vinyl acetate pressure. The relative slopes of these lines give the ratio of collision efficiencies A : He : H_2 = 1 : 0·6 : 0·5. If allowance is made for the different speeds, the collision efficiencies have the following values relative to argon : He 0·085, H_2 0·036. In passing it is worth noting that inert gases have absolutely no effect on the free-radical polymerisation.

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227. *Radical-sensitised Polymerisation of Vinyl Acetate Vapour.*

By H. W. Melville and R. F. Tuckett.

The kinetics of the polymerisation of vinyl acetate vapour initiated by hydrogen atoms and by methyl radicals has been investigated, with the following results. Owing to the fact that the direct photochemical polymerisation does not occur at room temperatures below 20 mm., the free-radical reaction can be studied alone by working at pressures below this limit. The reaction rate is proportional to the first power of the vinyl acetate pressure and to the square-root of the rate of production of radicals. The kinetic chain length of the reaction has been measured by the method of end-group analysis. The reaction has a high negative temperature coefficient.

These results show that the direct photo-reaction also proceeds by means of a radical mechanism, the correlation between the two reactions being close. The direct reaction initially involves the production of di-radicals which are subject to deactivation spontaneously or by collision with inert added gases. These gas-phase reactions exhibit the so-called gel effect to a maximum degree and thus the termination velocity coefficients are reduced to small values. This gives rise to overall apparent negative energies of activation.

In the previous paper it has been shown that vinyl acetate does not apparently undergo photochemical polymerisation at room temperature at pressures below 20 mm. In this respect it is unique but the phenomenon can be put to good use in the following way. With some molecules, *e.g.*, methyl methacrylate, it is comparatively easy to study the kinetics of the free-radical polymerisation without complications arising out of the occurrence of the direct photo-reaction; with other molecules like methyl acrylate this cannot conveniently be done for a variety of reasons. It is, however, important to study the kinetics of the radical reaction and thus characterise the type of polymerisation for purposes of reference so that by comparison it is possible to say whether or not the direct reaction, for example, goes by way of free radicals. At pressures below 20 mm. it proves to be possible to induce radical polymerisation and to study it to the complete exclusion of the direct reaction. The present paper describes the results obtained in this way.

The apparatus used was identical with that described in the previous paper. Special methods and modifications are described in the appropriate places.

Hydrogen-atom-sensitised Reaction.—Although molecular hydrogen is an inhibitor for the direct photo-polymerisation, it indirectly becomes a sensitiser if mercury vapour is present and instead of a high-pressure mercury lamp a low-pressure type emitting unreversed 2537 A. radiation is employed. This phenomenon is well marked below the limiting pressure where, of course, no direct reaction can be detected. There is no doubt the accelerating effect of hydrogen is due to its sensitised dissociation to atomic hydrogen, which adds on to vinyl acetate to give a free radical, thus initiating polymerisation. There are some complications in the use of this indirect method. Excited mercury atoms will be deactivated by vinyl acetate molecules as well as by hydrogen and thereby start off a mercury-sensitised polymerisation, as has been shown in the previous paper. Fortunately, there is a pressure limit to this reaction (below) and hence its contribution to the total observed rate of polymerisation can easily be eliminated. Even at low pressures, mercury atoms will still be deactivated by vinyl acetate. The fraction f_{H_2} of excited mercury atoms deactivated by hydrogen molecules is simply given by

$$f_{H_2} = \frac{\sigma_{H_2}^2[H_2]\mu_{H_2\text{-}Hg}^{-\frac{1}{2}}}{\sigma_{H_2}^2[H_2]\mu_{H_2\text{-}Hg}^{-\frac{1}{2}} + \sigma_{VA}^2[VA]\mu_{VA\text{-}Hg}^{-\frac{1}{2}}}$$

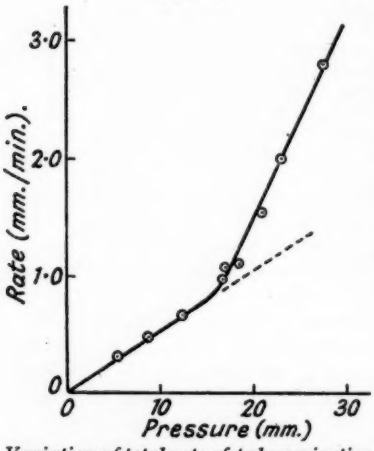
where σ is the sum of the quenching radii and μ is the reduced mass of the pairs of molecules concerned; $\sigma_{H_2}^2 = 6{\cdot}0 \times 10^{-16}$ cm.^{2} and σ_{VA}^2 is not known: it is probably about 20×10^{-16} cm.^{2}, for methyl methacrylate, for example, has $\sigma^2 = 25 \times 10^{-16}$ cm.^{2} (Bolland, unpublished experiments). This value being taken, it is calculated that $f_{H_2} = 0{\cdot}8$ for $H_2 : VA = 2{\cdot}3 : 1$, and $f_{H_2} = 0{\cdot}9$ for $H_2 : VA = 5{\cdot}8 : 1$. Consequently, high hydrogen pressures were invariably used to eliminate complication of the kinetics in the above manner. The reproducibility of the free-radical reaction is much better than that of the direct photo-reaction, mainly because of the shorter chain lengths involved. Although the rate of reaction does not immediately attain its maximum value in a clean tube, a very light coating suffices to prevent completely any wall termination. Corrections due to absorption of monomer by polymer are practically absent.

The mixtures of hydrogen and vinyl acetate were prepared in two ways. In one procedure the reaction vessel was filled with vinyl acetate to a given pressure. This was condensed out, the side tube cooled in liquid air, and then hydrogen admitted. In the second procedure vinyl

acetate was admitted first, followed by hydrogen, the pressure of which was maintained at a high value in its reservoir so that little if any vinyl acetate vapour could diffuse out into the hydrogen reservoir. The former method was the more convenient where it was necessary to measure accurately the initial pressure of the hydrogen rather than the total pressure of the mixture.

A pressure of 30 mm. of hydrogen being used, the variation of initial rate of polymerisation with pressure of vinyl acetate is shown in Fig. 1. In the first place it will be seen there is a marked acceleration in presence of hydrogen which can only occur because of the free-radical reaction induced by atomic hydrogen. Secondly, quite a fast reaction occurs at vinyl acetate pressures when the mercury-sensitised polymerisation of vinyl acetate does not proceed at all. At a pressure of 15 mm., however, this type of reaction seems to proceed in parallel with the hydrogen atom sensitised reaction. Below 15 mm. the free-radical reaction rate is proportional to the first power of the concentration of the acetate. Fig. 2 is a plot of the log of this rate as a function of radiation intensity. The slope of the line is 0·7, showing that quite a large proportion of the free radicals combines in the gas phase. Thus the kinetics are approximately expressed simply by

FIG. 1.



Variation of total rate of polymerisation with vinyl acetate pressure.

$$-\mathrm{d[M]/d}t = \text{const.}\ [\mathrm{M}]I^{\frac{1}{2}}$$

characteristic of a normal reaction in which mutual termination occurs and in which the rate of initiation is independent of monomer concentration. When individual runs are examined, however, and allowance is made for the disappearance of the appropriate amount of hydrogen, the first-order "constant" decreases with decreasing pressure as shown in Table I. Even a second-order "constant" exhibits a slight tendency to decrease. It is evident that this

TABLE I.

Temp. 15°. Hydrogen pressure 27·2 mm.

Time (mins.)	0.	1.	2.	3·5	5.	7.	9.	10.
Press. (mm.) of vinyl acetate, uncorr.	18·6	15·5	13·1	10·9	9·5	8·1	7·0	6·5
Press. (mm.) of vinyl acetate, corr. for loss of H_2	18·6	15·6	13·4	11·4	10·3	9·2	8·4	8·1
k (min.$^{-1}$) (1st order)	—	0·177	0·164	0·140	0·118	0·100	0·088	0·083
k (min.$^{-1}$ mm.$^{-1}$) (2nd order)	—	0·0100	0·0105	0·0095	0·0086	0·0079	0·0072	0·0070

diminution in velocity must be due to the accumulation of some rate-retarding molecule produced as a result of secondary reactions.

The addition of hydrogen actually inhibits the mercury photosensitised polymerisation since the hydrogen molecule deactivates quite a proportion of the excited mercury atoms. In fact it is possible to obtain an approximate estimate of the quenching radius of the vinyl acetate molecules from such data. Table II gives the relevant data for low vinyl acetate pressures.

TABLE II.

Monomer pressure (mm.)	18·0	22·3
Rate of mercury-sensitised reaction	0·9	2·2
Total rate of reaction with 30 mm. of hydrogen	1·00	1·85
Estimated rate of Hg-sensitised reaction in presence of hydrogen	0·79	0·66
Fraction of H_2 molecules deactivating excited Hg atoms (f_{H_2})	0·79	0·69

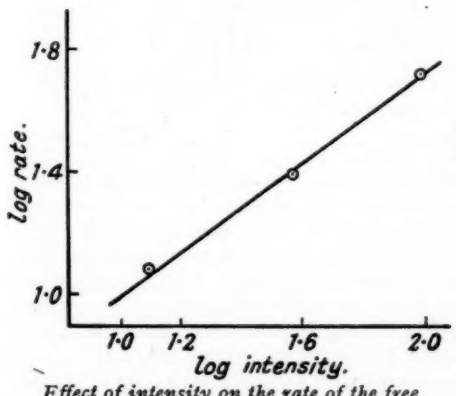
At a pressure of 18·0 mm. the mercury-sensitised rate is reduced from 0·9 to 0·19 mm./min., since a fraction f_{H_2} of the mercury atoms is deactivated by hydrogen. The value of f_{H_2} at 22·3 mm. is 0·69. But f_{H_2} is given by the equation

$$f_{H_2} = \frac{\sigma_{H_2}[H_2]/[VA] \cdot \mu_{H_2\text{-}Hg}^{-\frac{1}{2}}}{\sigma_{H_2}[H_2]/[VA]\mu_{H_2\text{-}Hg} + \sigma_{VA}^{2}\mu_{Hg\text{-}VA}^{-\frac{1}{2}}}$$

If σ_{H_2} is taken as $6{\cdot}0 \times 10^{-16}$ mm.^{2}, tnen since $[H_2]/[VA]$ is known, σ_{VA-H_2} may be computed. The figures are 20 and 25×10^{-16} mm.^{2}, respectively, in good agreement with the experimentally determined value of 25×10^{-16} mm.^{2} for methyl methacrylate.

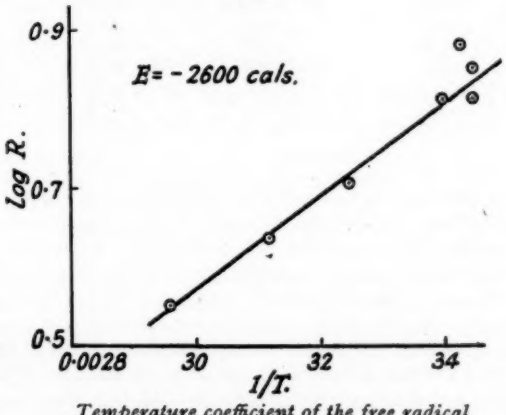
Inhibitors.—Although an examination of the course of an individual run showed unmistakable evidence of the production of an inhibitor, more direct evidence was desirable. This was obtained in the following manner. Unfortunately, the constant pressure–variable volume method cannot be used, but a modification is possible. A mixture of monomer and hydrogen at a suitable pressure is irradiated for such a time that 2 mm. of vinyl acetate are polymerised. The gases are then thoroughly mixed by moving the mercury in the gas burette, and the pressure is adjusted so that the original vinyl acetate pressure is obtained. Next, another 2 mm. of vinyl acetate are polymerised and the time is noted. If no inhibitor had been produced the

FIG. 2.



Effect of intensity on the rate of the free radical reaction.

FIG. 3.



Temperature coefficient of the free radical reaction.

time should have been slightly shorter because of the slight diminution in volume of the system. Table III shows that, in fact, these times for 2 mm. polymerisation increased continually.

TABLE III.

Vinyl acetate 18·8 mm. Hydrogen 24·2 mm.

Initial vol. of system (c.c.) ...	210	198	187	176	167	159	150
Time (mins.) for $-\Delta p = 2$ mm.	1·23	1·18	1·63	2·58	3·50	4·75	6·75

Further conclusive proof of the presence of an inhibitor can be obtained by examining the intensity exponent, which should increase as inhibitor accumulates. This is best done by carrying out two runs with different intensities and comparing the ratio of times required for the same pressure decrease throughout the course of the reaction. The following results were obtained in two such runs.

Ratio of intensities 8·0 : 1. Vinyl acetate 19·0 mm. Hydrogen 27·5 mm.

Pressure range (mm.)	18—11	6·0—3·5	4·5—3·5
Ratio of times	2·3	3·16	3·8

The increase in ratio shows that the exponent is increasing from about 0·5 towards unity at the end of the run.

The inhibitor is not produced by short-wave radiations from the 2537 A. lamp, for an acetic acid filter does not cut down inhibitor production. It is condensable in liquid air and solid carbon dioxide. This was shown by condensing the contents of the reaction vessel after a run into a suitable trap and pumping off all non-condensable gas. Fresh hydrogen was then added, and the run continued. At − 183° and − 80° the inhibitor was retained in the trap.

Temperature Coefficient.—The temperature coefficient of the free-radical reaction can only be studied over a comparatively small range since at higher temperatures the direct reaction begins to make its appearance and thus complicates the interpretation of the kinetics. Fig. 3 shows how the rate varies with temperature, the rate being measured by taking the reciprocal of the time for the pressure of vinyl acetate to fall 4 mm. It will be seen that the temperature

coefficient is negative, with a value of − 2600 cals. So far as is known, the addition of atomic hydrogen to an unsaturated molecule proceeds with such a small energy of activation that the temperature coefficient of the polymerisation process must certainly be due to that of the propagation and termination reactions. Since the polymerisation ends by mutual destruction of active molecules, the apparent energy of activation is equal to $E_p - \frac{1}{2}E_T$, E_p and E_T being the energies of activation for propagation and termination. These temperature coefficients were measured at different intensities and the results are given in Table IV.

TABLE IV.

Chain length at 17°:

8.		12.		50.	
Temp.	τ (mins.) for $\Delta p = 4$ mm.	Temp.	τ (mins.) for $\Delta p = 4$ mm.	Temp.	τ (mins.) for $\Delta p = 4$ mm.
17·5°	4·00	17·0°	6·25	18·0°	10·0
19·5	3·6	18·6	5·3	19·0	11·4
25·0	5·2	21·3	6·2	32·0	19·7
35·5	4·3	34·5	7·9	48·0	38·4
55·0	5·5	47·6	9·3	—	—
—	—	65·0	11·2	—	—
$E = -1900$ cals.		$E = -2600$ cals.		$E = -8200$ cals.	

This reaction thus falls into line with the direct photo-polymerisation and with the polymerisation of methyl acrylate and of methyl vinyl ketone in the gas phase in that negative energies of activation are observed. With the free-radical reaction it is probable that the value would not change with further increase in chain length. The mere fact that the value is negative would imply that E_T is greater than E_p by a substantial amount. This fact is anomalous since it would imply that the two free radicals must become activated before they react with each other; in other words, more activation energy is required for the interaction of two radicals than is required for the interaction between a radical and a double bond. Such a state of affairs is hardly conceivable, but there appears to be no valid alternative explanation. The variation of the apparent energy of activation with chain length may quite well be due to a variation in E_p or E_T, especially when the chain length is so short.

Chain Length.—If after a hydrogen-atom-sensitised polymerisation all the vinyl acetate vapour is condensed out by passing the mixture through a trap cooled in liquid air, the hydrogen pressure is less than that at the start of the run. For example, with 18·6 mm. of vinyl acetate and 27·15 mm. of hydrogen a time of illumination of 10 mins. gives a total pressure decrease of 12·3 mm., the hydrogen pressure being now 25·85 mm. The reason for the small fall in pressure is that the hydrogen atom responsible for starting polymerisation is incorporated in the polymer itself. Thus the decrease may be made the basis of measuring the kinetic chain length of the reaction and therefore the number average molecular weight of the polymer.

Owing to the small pressure decrease certain precautions have to be taken. Only tubes lightly coated with polymer may be used since atomic hydrogen may reduce the polymer and so be removed in a non-polymerisation reaction. The most convenient method of measuring the decrease in hydrogen pressure consists in admitting the appropriate amount of vinyl acetate, freezing this out, and then admitting hydrogen. After the run the vinyl acetate is once more frozen out, and the hydrogen pressure measured. After correction for the cooling of the trap, the decrease in pressure of hydrogen is subtracted from the total observed pressure decrease to give the diminution in vinyl acetate pressure.

In considering the kinetics of the reaction as a whole it is necessary first to determine whether there is any possibility of a hydrogen atom terminating polymerisation as well as starting it. If this kind of termination occurred exclusively, then it can be shown (Melville, *Proc. Roy. Soc.*, 1937, *A*, **163**, 511) that $R \sim$ const. $[M]^2$, the rate being independent of intensity. Since the observed kinetics are $R \sim$ const. $[M]I^{\frac{1}{2}}$, it is evident that this kind of termination does not enter into the question. As has been seen in Table IV, the kinetic chain length is comparatively short, and this introduces a slight complication. The general expression for the concentration of the active polymer is

$$d[P]/dt = I - k_t[P]^2 = 0$$

where $I = k[H][M]$, k being the bimolecular coefficient for the reaction of hydrogen atoms with the monomer. For short chains, then

$$-d[M]/dt = I + I^{\frac{1}{2}}[M]k_p/k_t$$

Thus the rate will not be strictly proportional to the square-root of the intensity. The deviation may be computed in the following way. Suppose $-\mathrm{d[M]/d}t \sim I^x$; then for two intensities

$$x = [\log R_2/R_1)]/[\log (I_2/I_1)]$$

Let $I_2/I_1 = 8$, as was used in some experiments, then, if $\delta = k_t/k_p$,

$$x \log 8 = \log \frac{I_2 + [\mathrm{M}]\delta^{-1}I_2^{\frac{1}{2}}}{I_1 + [\mathrm{M}]\delta^{-1}I_1^{\frac{1}{2}}}$$

$$= \log \sqrt{8} + \log \frac{\nu_2}{\nu_2 - 0{\cdot}65}$$

where ν_2 is the chain length at intensity I_2; or

$$x = 0{\cdot}50 + 1{\cdot}11 \log \nu_2/(\nu_2 - 0{\cdot}65)$$

Hence x may be obtained for various different values of ν_2 as follows:

$\nu_2 =$	4	5	6	12	∞
$x =$	0·586	0·567	0·55	0·53	0·500

For example, with a vinyl acetate pressure of 19 mm. and $H_2 = 27{\cdot}5$ mm. at 17°, the chain length is greater than 10 for full intensity and over 30 at the 0·125 full intensity x (experimental) = 0·47.

Independent evidence also indicates mutual termination of polymer growth. In such a mechanism the chain length should be inversely proportional to the square-root of the intensity of incident light. Instantaneous values of the chain length cannot, of course, be computed because of the impossibility of measuring accurately small decreases in hydrogen pressure; hence the following procedure was adopted. The hydrogen–vinyl acetate mixture is illuminated, and the chain length measured by the above-mentioned method. A second measurement is made by resuming the run. In this way the corrected vinyl acetate pressure–time curve is constructed. The rate of polymerisation at say two given pressures can then be read off. The rate of hydrogen loss is assumed to be the average rate of loss over the run. The whole procedure is then repeated at a lower intensity. The results in Table V show the expected dependence of chain length on intensity, and the observed figures are in reasonably good agreement with the theoretical values calculated from the ratio of the intensities.

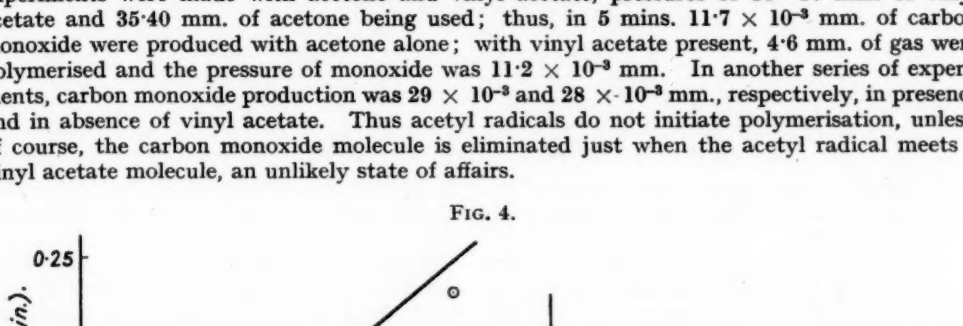
TABLE V.

Intensity.	Chain length at vinyl acetate pressures (mm.) of:		Ratio of chain lengths obs. at vinyl acetate pressures (mm.) of:		Calculated ratio of chain lengths.
—	13·0	6·0	13·0	6·0	—
1·00	13·5	2·7	3·6	2·5	2·83
0·125	49	6·8	—	—	—

Methyl-radical-sensitised Reaction.—Hydrogen atoms are not always the most suitable type of initiator for a free-radical reaction. In addition, it has been shown with butadiene, for example (Jones and Melville, *Proc. Roy. Soc.*, 1946, *A*, **187**, 87), that whereas methyl radicals initiate polymerisation, hydrogen atoms lead to hydrogenation of the butadiene. It was therefore desirable to see whether methyl radicals from photodecomposing acetone could effect polymerisation of vinyl acetate vapour and so find whether the kinetics of the two reactions are identical. With acetone as a source of methyl radicals there is a very marked acceleration of polymerisation, for at 22 mm. vinyl acetate pressure the rate was 0·02 mm./min. but on addition of 40 mm. of acetone the rate jumped to 0·45 mm./min. Even well below the critical limit with VA = 16 mm., the rate was 0·22 mm./min., the rate of the direct reaction being negligible. In Fig. 4 the kinetics are briefly summarised. In Fig. 4(*a*) it will be seen that the rate is proportional to pressure, the upper limit of pressure being fixed by the limit for the direct reaction. In Fig. 4(*b*) log rate is plotted against log intensity. The slope of the straight line is 0·46. Thus the kinetics of the hydrogen-atom- and of the methyl-radical-sensitised reaction are exactly similar. There is, however, a further interest in this similarity. If matters are so adjusted that the two reactions occur at the same speed, then the chain length must be identical and the rate of initiation must also be identical. But the rate of production of hydrogen atoms is known, and hence it should in principle be possible to measure the rate of production of methyl radicals from acetone, and thus throw some further light on the photochemistry of this molecule. Much has already been written about the photochemistry

of acetone, and it is usually presumed that when the molecule does dissociate the first act is the production of acetyl and methyl radicals and that the former subsequently decompose to methyl and carbon monoxide, though under some conditions they may combine to diacetyl. In a recent paper evidence is presented to show that apparently the excited acetone molecule may decompose to fragments of ethane and carbon monoxide *without* the production of radicals. The production of acetyl does complicate matters. In some acetone-catalysed polymerisations (Jones and Melville, *loc. cit.*) it has been found that the rate of production of carbon monoxide from acetone is diminished when monomer is present. This would imply that the acetyl radical reacts with the monomer before it has time to decompose. Similar experiments were made with acetone and vinyl acetate, pressures of 16—17 mm. of vinyl acetate and 35·40 mm. of acetone being used; thus, in 5 mins. $11{\cdot}7 \times 10^{-3}$ mm. of carbon monoxide were produced with acetone alone; with vinyl acetate present, 4·6 mm. of gas were polymerised and the pressure of monoxide was $11{\cdot}2 \times 10^{-3}$ mm. In another series of experiments, carbon monoxide production was 29×10^{-3} and 28×10^{-3} mm., respectively, in presence and in absence of vinyl acetate. Thus acetyl radicals do not initiate polymerisation, unless, of course, the carbon monoxide molecule is eliminated just when the acetyl radical meets a vinyl acetate molecule, an unlikely state of affairs.

FIG. 4.



(a) *Effect of pressure on the methyl-radical-sensitised reaction.*
(b) *Effect of intensity on the radical-sensitised reaction.*

The experimental procedure is somewhat complicated. First of all two lamps are used, the first a low-pressure lamp emitting the 2537 A. line to dissociate the hydrogen, the second a high-pressure lamp to dissociate the acetone. The distances of these lamps from the reaction vessel are so adjusted that with a given acetone pressure the rates of polymerisation are the same. First, a hydrogen atom run is made, the chain length being measured at two points. Next another hydrogen atom run is made for approximately half the period, and the chain length re-measured. Acetone is then admitted to a pressure of 50 mm. The hydrogen pressure is then measured again since a small amount escapes on introduction of the acetone. The hydrogen–vinyl acetate–acetone mixture is then irradiated with the high-pressure lamp for a time such that polymerisation occurs to the same extent as with the first hydrogen atom run. The data from the first run then give the hydrogen molecule consumption during the second part of the run. Finally, the vinyl acetate and acetone are condensed out, and the total pressure due to hydrogen and to carbon monoxide is measured.

By this method it was found over the same range of vinyl acetate pressures, *viz.*, 17·5—12·5 mm., that the carbon monoxide produced from the photodecomposing acetone was equal to volume of hydrogen consumed in the corresponding part of the hydrogen run. The data for a run of this type are given below.

Vinyl acetate = 22·0 mm. Hydrogen 35·0 mm. Acetone 50·0 mm.

Type of run.	Rate of 1st half of polymerisation.	Rate of 2nd half of polymerisation.	
Me	1·38	0·80	0·25 mm. CO produced
H	1·32	0·73	0·30 mm. H_2 consumed
Me	1·46	0·98	0·25 mm. CO produced

General Discussion of the Vinyl Acetate Reaction.

It now remains to discuss and compare the free-radical and the direct polymerisation reactions. The former is at first sight the simpler, for the mechanism consists in the addition of the hydrogen atom or methyl radical to the vinyl acetate molecule to form another free radical, to which are subsequently added further vinyl acetate molecules until two of these comparatively large free radicals interact. It is not yet certain whether this results in combination or disproportionation. The anomalous feature of this and other gas-phase reactions is the negative temperature coefficient. This may be due to a variety of factors. First, even if the radical polymers are small, it may be that in course of growth a new solid phase appears with the consequence that monomer will presumably be adsorbed on this growing particle as a necessary preliminary to addition. The rate of polymerisation will then be proportional to the concentration of monomer in the polymer particle. Increase of temperature will consequently decrease this concentration so that this factor alone will give rise to an apparent negative temperature coefficient. Second, quite a different factor may also give rise to a diminished temperature coefficient. It has now been established (Burnett and Melville, *Nature*, **1946**, **158**, 553) that when polymerisation of vinyl acetate occurs in a solvent such as hexane in which the polymer is not very soluble, the effect of precipitating out the growing polymer is to diminish the magnitude of the bimolecular reaction coefficient for the termination of polymer growth. The coefficient which is not normally affected by temperature acquires in these circumstances a positive temperature coefficient. A similar precipitation will occur even more readily in the gas phase. It is not therefore suprising that an overall negative temperature coefficient is observed, and that the larger the kinetic chain length the higher the value of the negative energy of activation. It is possible that both factors operate together.

With the direct reaction at sufficiently high pressures, the general kinetics are similar to those of the pure radical reaction. For comparable rates of initiation the overall polymerisation velocities of the radical and of the direct reaction are quite similar. It would therefore seem probable that the direct reaction also proceeds by a free-radical mechanism. The problem then is to understand why the critical pressure limit and inert gas effects make their appearance. The matter is most satisfactorily accounted for if it is assumed that absorption of ultra-violet light by monomer results in the production of a di-radical. Such a radical is simply an electronically excited molecule. The results show clearly that such a molecule can spontaneously give up its electronic energy or give it up to an inert gas at quite low pressures. At high enough pressures, however, further monomer molecules will add on to both ends of this di-radical. It is unfortunate that the photopolymer is made insoluble by some secondary reactions and thus its molecular weight cannot be compared with that of the free-radical polymer. The negative temperature coefficient of the direct reaction then is explained in a similar manner to that of the radical reaction.

Experimental evidence has been given elsewhere to suggest that the polymerisation of vinyl acetate in the liquid phase or in solution goes by way of free radicals. Here there should be an exact correlation between the reaction in the two phases. The obstacle to establishing a numerical correlation is due wholly to the so-called gel effect, *i.e.*, to the influence of environment or polymer shape on the velocity coefficient for the termination of molecular growth. In the liquid phase precisely similar overall kinetics are observed, but it is evident that the magnitudes of the velocity coefficients cannot be compared. For the gas phase the termination coefficient will not have its maximum value but some lower and ill-defined value. For these reasons the liquid-phase reaction with either pure monomer or monomer in a good solvent is far simpler than the gas-phase reaction.

The experiments described in this and the preceding paper were carried out in 1938—39 in the Colloid Science Department, The University, Cambridge. We should like to thank Professor E. K. Rideal for his great encouragement and interest in this work. These researches were made possible owing to the generosity of Aero Research Limited, Duxford, Cambridgeshire, who kindly provided a maintenance grant to one of us (R. F. T.).

THE UNIVERSITY, ABERDEEN. [*Received, December 5th*, 1946.]

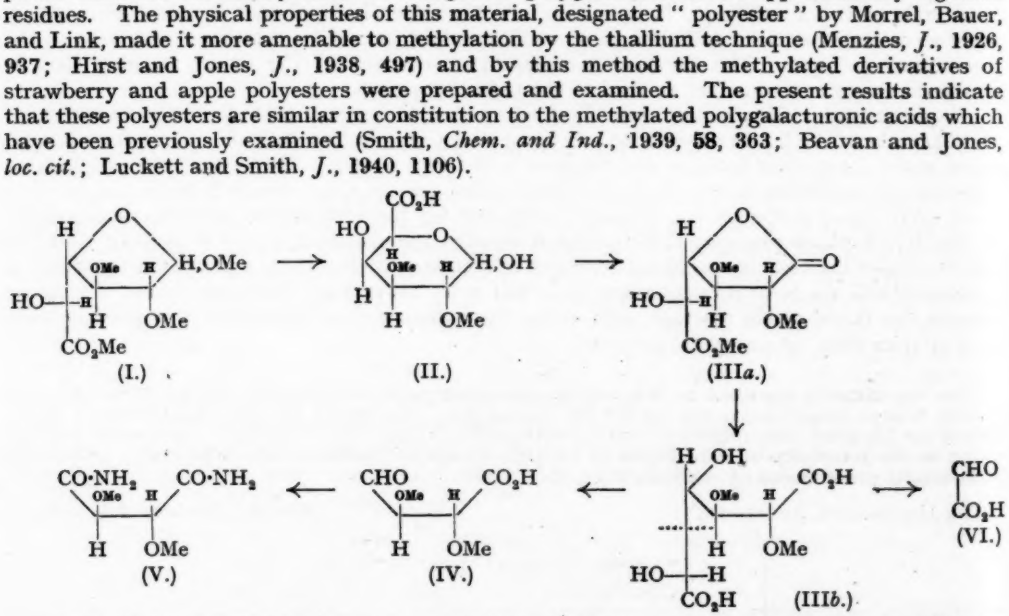
228. *Pectic Substances. Part V. The Molecular Structure of Strawberry and Apple Pectic Acids.*

By G. H. Beavan and J. K. N. Jones.

Degradation products prepared from strawberry pectin and apple pectin by boiling with methanolic hydrogen chloride have been converted into their methylated derivatives. Hydrolysis of the latter with methanolic hydrogen chloride yielded the methyl ester of 2 : 3-dimethyl methyl-*d*-galacturonoside as the main product. The bearing of these observations on the chemical structure of pectic acid is discussed.

Pectins commonly occur in fruit and have been the subject of chemical investigation by many workers, and it is now generally accepted that they are mixtures of polysaccharides, amongst which galactan, araban, and polygalacturonosides predominate (for a review of the evidence see the article by Hirst and Jones, " Advances in Carbohydrate Chemistry ", Vol. II, 1946). These polysaccharides are in close physical union, and great difficulty is experienced in separating the components in a pure condition, particularly those of the polygalacturonoside fraction. Arabans from peanut, apple, and citrus pectins have been shown to consist of *l*-arabofuranose residues linked to form a branched chain polymer (Hirst and Jones, *J.*, 1938, 496; 1939, 453, 454; Beavan, Hirst, and Jones, *J.*, 1939, 1865), whilst the galactan from *Lupinus albus* consists of β-*d*-galactopyranose residues in the form of a linear polymer (Hirst, Jones, and Walder, *J.*, forthcoming publications). These two polyssaccharides could not therefore be derived one from the other by oxidation and decarboxylation at C_6 of the pyranose residues. In view of these results it became of special interest to determine whether any correlation exists between the structures of the pectic acid and of either of the polysaccharides associated with it, and whether pectic acids from different sources possess similar structures.

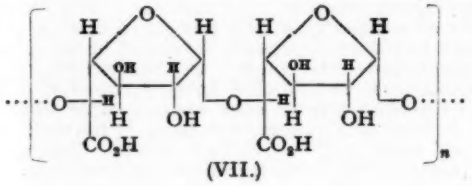
The investigation of the pectic acid component was rendered all the more difficult by reason of the special physical and chemical properties of the polysaccharide. In a previous publication (Beavan and Jones, *Chem. and Ind.*, 1939, **58**, 363) attention was drawn to the difficulties encountered in methylating pectic acid both by the methyl sulphate and by the thallium methylation technique. This difficulty was in part overcome by methylating a degraded pectic acid derivative prepared by boiling crude pectin with methyl alcoholic hydrogen chloride (Morrel, Bauer, and Link, *J. Biol. Chem.*, 1935, **105**, 1; Hirst, Jones, and Jones, *J.*, 1939, 1880). This procedure destroyed the more labile araban and galactan and converted the pectic acid into the methyl ester of a degraded polygalacturonide of approximately eighteen residues. The physical properties of this material, designated " polyester " by Morrel, Bauer, and Link, made it more amenable to methylation by the thallium technique (Menzies, *J.*, 1926, 937; Hirst and Jones, *J.*, 1938, 497) and by this method the methylated derivatives of strawberry and apple polyesters were prepared and examined. The present results indicate that these polyesters are similar in constitution to the methylated polygalacturonic acids which have been previously examined (Smith, *Chem. and Ind.*, 1939, **58**, 363; Beavan and Jones, *loc. cit.*; Luckett and Smith, *J.*, 1940, 1106).



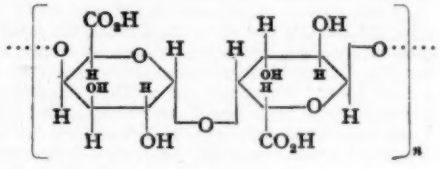
Proof of the constitution of the methylated polyester was furnished by the following observations : the methylated polyuronide gave, on hydrolysis with methyl alcoholic hydrogen

chloride under pressure, 2 : 3-dimethyl methyl-*d*-galacturonoside methyl ester (I) as a mixture of its pyranose and furanose forms (cf. Luckett and Smith, *loc. cit.*). On hydrolysis with aqueous acid (I) was converted into 2 : 3-dimethyl *d*-galacturonic acid (II) identified after oxidation and esterification as the crystalline γ-lactone methyl ester (III*a*) of 2 : 3-dimethyl *d*-mucic acid (III*b*). The constitution of this crystalline product followed from its reaction with periodic acid, which gave the half-aldehyde of *l*(+)-dimethoxysuccinic acid (IV), identified as *l*(+)-dimethoxysuccinamide (V), and glyoxylic acid (VI), identified by its colour reaction with casein and sulphuric acid.

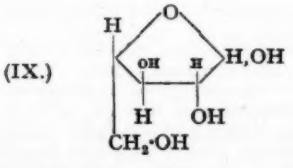
The polyester from both strawberry and apple pectin must therefore be a polymer built up of *d*-galacturonic acid residues in which the hydroxyl groups on C_2 and C_3 are free. The two structures which are in agreement with this evidence are (VII) and (VIII), of which the pyranose form (VIII) is by far the more probable since the pyranose structure alone would display the resistance to acidic hydrolysis so characteristic of the pectic acid molecule. That the linkage



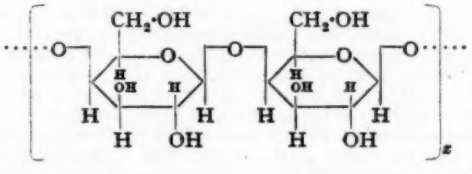
(VII.)



(VIII.)



(IX.)



(X.)

between the galacturonic acid residues is of the α-type is shown by the high positive rotation of pectic acid. It is clear, therefore, that a polygalacturonide with this structure cannot be transformed directly by decarboxylation at C_6 into an araban of the type found associated with pectic acid, since this araban is known to possess a branched chain structure of *l*-α-arabofuranose residues (IX) linked to each other in three different ways—namely, through C_1 (A1 . . . .), through C_1 and C_5 (. . 5A1 . .), and through C_1C_2 and C_5 (:::$^{5}_{5}$A1 . . .). Nor can the pectic acid arise from the galactan (X) by oxidation of the primary alcohol groups, since the sugar residues in (X) are linked by β-links. It follows, therefore, that if galactan (X) is the source of araban, then hydrolysis followed by re-synthesis of the oxidised and decarboxylated sugar must intervene.

Experimental.

Strawberry Pectic Acid.—The pectin was obtained from strawberry juice, for a supply of which we wish to express our thanks to Dr. V. L. S. Charley and Carter and Co. of Bristol. The crude pectin was contaminated with kieselguhr; it was triturated with 90% alcohol and filtered to remove colouring matter. The solid was dried at 40°/12 mm. and extracted with the calculated quantity of dilute sodium hydroxide solution. The sludge was spun on the centrifuge and the top clear, light blue solution poured with stirring into 5 vols. of 90% alcohol acidified with hydrochloric acid. Pectic acid was precipitated; it was filtered off, washed with alcohol until free from hydrochloric acid, and dried under reduced pressure; $[\alpha]_D^{20°}$ + 251° (in neutral aqueous solution) [Found: Uronic anhydride, 84·0 (calc. from the yield of carbon dioxide evolved on boiling with 12% hydrochloric acid); pentosan, 4·1 (calc. from the yields of furfuraldehyde and carbon dioxide evolved on boiling with 12% hydrochloric acid); galactan, 9·9 (by difference); OMe, 0·2%; equiv., 225].

Strawberry Pectin Polyester (see Morrel, Bauer, and Link, *loc. cit.*).—Strawberry pectic acid (100 g.) was refluxed with stirring with 3% methyl alcoholic hydrogen chloride (1 l.). After 24 hours sufficient concentrated methyl alcoholic hydrogen chloride was added to bring the concentration up to 5% and the refluxing continued for a further 66 hours. The cooled reaction mixture was spun on the centrifuge and the dark slimy solid thus obtained washed with methyl alcohol until free from hydrogen chloride. The solid was dried at 60°/12 mm. and then extracted thrice with boiling water (500 c.c.). The extracts were spun on the centrifuge and the clear solution was poured into alcohol (2½ l.). The precipitated polyester (65 g.) was separated on the centrifuge, washed with alcohol and acetone, and dried at 50°/12 mm.; $[\alpha]_D^{20°}$ + 234° (*c*, 1·2) (Found: OMe, 17·4%; equiv., 200).

A sample of the polyester was titrated with the calculated quantity of barium hydroxide and the resulting barium *salt* precipitated with alcohol. The white solid was filtered off, washed with alcohol,

and dried in a vacuum (Found: Ba, 25·1; OMe, 1·8. A methylpolygalacturonoside methyl ester containing eight units requires Ba, 27·7; OMe, 1·6%).

Methylation of Strawberry Polyester.—The polyester (5·7 g.) was dissolved in water (20 c.c.) and to it was added a hot concentrated solution of thallium hydroxide (30 c.c. of 6N). The cream-coloured precipitate was filtered off, washed with methyl alcohol and ether, and dried at 40°/12 mm. The orange solid was ground to a powder (120 mesh) and boiled with methyl iodide for 72 hours under reflux with the exclusion of light and moisture. Excess of methyl iodide was distilled off and the residue extracted exhaustively with methyl alcohol. The extracts on concentration gave partially methylated strawberry polyester as a pale brown solid (4·6 g.). The partially methylated material was dissolved in alcohol and evaporated to dryness with the addition of a benzene solution of thallous ethoxide (5 equivs.). The resulting brown solid was powdered (120 mesh) and boiled with methyl iodide until the thallium iodide was neutral to litmus. Methylated strawberry polyester was isolated, as described above, as a stiff brown syrup (4·35 g.) (Found: OMe, 42·4%). The syrup was separated into two fractions by precipitation from a chloroform solution with ether. (A) Ether-insoluble (2·15 g.); $[\alpha]_D^{20°}$ + 144° (*c*, 0·66 in methyl alcohol) (Found: OMe, 39·9%. A dimethyl uronic methyl ester polymer requires OMe, 42·7%). (B) A stiff brown syrup obtained on evaporation of the ethereal extract (2·20 g.), which was not further examined.

Hydrolysis. The methylated polyester was extremely resistant to hydrolysis, but this could be effected by the use of methyl alcoholic hydrogen chloride under pressure. The material (2·10 g.) was dissolved in 3% methyl alcoholic hydrogen chloride (35 c.c.) and heated at 140° in a sealed tube for 24 hours. The hydrolysis mixture was nearly neutral and a considerable pressure developed in the tube owing to the formation of methyl chloride and carbon dioxide. The solution was neutralised with silver carbonate, filtered, and evaporated under diminished pressure to a dark brown syrup (1·85 g.). This was separated into two fractions by extraction with ether—(1) an ether insoluble-solid which consisted of incompletely hydrolysed material, and (2) an ether-soluble syrup consisting of the methyl ester of 2:3-dimethyl methyl-*d*-galacturonoside [1·5 g., $n_D^{18°}$ 1·473, $[\alpha]_D^{20°}$ − 27° (in acetone)]. This was fractionally distilled in a vacuum giving: (*a*) the methyl ester of 2:3-dimethyl methyl-*d*-galacturonoside (0·90 g.), b. p. 150°/0·001 mm. (bath temp.), $n_D^{19°}$ 1·4618, $[\alpha]_D^{21°}$ − 38° (*c*, 3·0 in water) (Found: OMe, 48·2; equiv., 254. Calc. for $C_{10}H_{18}O_7$: OMe, 49·6%; equiv., 250); (*b*) a fraction, b. p. 180°/0·01 (0·3 g.), $n_D^{19°}$ 1·4738, which was partly crystalline, the crystals which separated after tiling having m. p. 211° not raised on recrystallisation from ether; (*c*) still residue (0·3 g.).

The distilled ester (0·87 g.) was hydrolysed with N-hydrochloric acid (30 c.c.) at 90—95°: $[\alpha]_D^{21°}$ − 38° (initial value); + 31° (25 minutes); + 52° (1 hour); + 59° (1½ hours, constant value). The solution was neutralised with silver carbonate and filtered before and after the passage of hydrogen sulphide. Removal of the solvent at 40°/12 mm. left 2:3-dimethyl *d*-galacturonic acid (0·8 g.), $[\alpha]_D^{20°}$ + 63° (*c* 1·11 in water) (Found: OMe, 25·9: equiv., 212. Calc. for $C_8H_{14}O_7$: OMe, 27·9%; equiv., 222), which was oxidised with bromine water; the resultant 2:3-dimethyl *d*-mucic acid (0·8 g.) was isolated as a syrup, $[\alpha]_D^{21°}$ − 20° (*c*, 0·99 in methyl alcohol) (Found: OMe, 25·0; equiv., 122. Calc. for $C_8H_{14}O_8$: OMe, 26·9%; equiv., 119). The acid (0·70 g.) was esterified by boiling with 2% methyl alcoholic hydrogen chloride for 15 hours. The cooled solution was neutralised with silver carbonate, filtered, and evaporated to a syrup, which was extracted with ether. The solvent was distilled off, leaving the syrupy ester (0·72 g.), $n_D^{18°}$ 1·4688, $[\alpha]_D^{20°}$ − 5° (*c*, 0·78 in methyl alcohol) (Found: OMe, 38·8%), a portion of which (0·40 g.) was distilled under reduced pressure giving the methyl ester of the 1:4-lactone of 2:3-dimethyl *d*-mucic acid (0·33 g.), b. p. 160°/0·001 mm. (bath temp.), $n_D^{18°}$ 1·4658, $[\alpha]_D^{20°}$ − 40° (in water) (Found: equiv., 118). This crystallised on standing and was recrystallised from ether. It had m. p. 77—78°, raised to 96° on drying in a vacuum (Found, on a dried sample: C, 46·2; H, 5·8; OMe, 38·4. Calc. for $C_9H_{14}O_7$: C, 46·2; H, 6·0; OMe, 39·7%).

The ester lactone (0·26 g.), m. p. 96°, was oxidised with the calculated quantity of periodic acid in water (10 c.c.): $[\alpha]_D^{22}$ − 40° (initial value); − 10° (5 minutes); + 12° (12 hours, constant value). The solution was neutralised with barium carbonate, filtered, and concentrated to about 5 c.c. A small portion of the solution at this stage gave with casein and sulphuric acid a strong positive test for glyoxylic acid. Barium carbonate (1 g.) and bromine (1 c.c.) were added to the solution which became non-reducing towards Fehling's solution after 12 hours. The solution was aerated to remove excess of bromine and filtered. The filtrate was evaporated to dryness and the residue esterified by boiling with 2% methyl alcoholic hydrogen chloride (90 c.c.). The cooled solution was neutralised with silver carbonate and filtered, and the solvent evaporated at 60°/12 mm. The solid residue was exhaustively extracted with ether and the extracts were concentrated in a vacuum to a syrup (0·20 g., $n_D^{20°}$ 1·4348) which was distilled giving the dimethyl ester of *l*(+)-dimethoxysuccinic acid (0·15 g.), b. p. 90—110°/0·001 mm. (bath temp.), $n_D^{21°}$ 1·4322, $[\alpha]_D^{20°}$ + 77° (*c*, 2·46 in methyl alcohol) (Found: OMe, 58·2. Calc. for $C_6H_{14}O_6$: OMe, 60·2%). The ester (120 mg.) with methyl alcoholic ammonia gave needle-shaped crystals of the diamide of *l*(+)-dimethoxysuccinic acid (75 mg.), m. p. and mixed m. p. 280° (decomp.), $[\alpha]_D^{20°}$ + 96° (*c*, 0·73 in water).

Apple Pectin Polyester.—Apple pectic acid (Hirst and Jones, *J.*, 1939, 456) (uronic anhydride, 73·0; OMe, 10·2%; equiv., 250; $[\alpha]_D^{23°}$ + 230°) was converted by boiling with methyl alcoholic hydrogen chloride in the usual manner into the polyester which was isolated, as described above, as a snow-white powder. Yield, 65%; $[\alpha]_D^{20°}$ + 226° (in neutral aqueous solution) (Found: OMe, 17·4%; equiv., 195). A sample of the polyester was treated with the calculated quantity of barium hydroxide and the resulting barium salts were precipitated by alcohol. The white solid was filtered off, washed with alcohol, and dried in a vacuum (Found: Ba, 24·6; OMe, 1·5. A methylpolygalacturonoside methyl ester containing eight units requires Ba, 27·7; OMe, 1·6%).

Methylation. The polyester (6·0 g.) was dissolved in water (30 c.c.) and a hot solution of 2N-thallous hydroxide (100 c.c.) was added. The precipitated white thallium derivative was filtered off, washed with alcohol and ether, and dried at 60°/12 mm. The powdered solid (120 mesh) was boiled with methyl iodide under reflux with the exclusion of light and moisture until the solid no longer had an alkaline

reaction. The solution was worked up as described for the strawberry polyester. Two further methylations with thallous ethoxide solution gave methylated apple polyester as a syrup (5·4 g.). This was dissolved in chloroform and separated by the addition of ether into (*a*) a crisp brown solid {1·8 g., $[\alpha]_D^{20°}$ + 146° (in methyl alcohol); OMe, 39·9%}, and (*b*) a syrup which was not further examined.

Hydrolysis. Methylated apple polyester (1·10 g.) was dissolved in 4% methyl alcoholic hydrogen chloride (25 c.c.) and heated under pressure at 140—150° for 24 hours. The cooled solution was neutralised with silver carbonate, filtered, and evaporated to a syrup (0·95 g.) which was exhaustively extracted with ether. Evaporation of the ether left a syrup (0·80 g.), $n_D^{21°}$ 1·4842, $[\alpha]_D^{20°}$ − 15° (*c*, 1·0 in acetone), which was distilled in a vacuum giving: (1) 0·10 g., b. p. up to 130°/0·001 mm. (bath temp.), $n_D^{21°}$ 1·4805; (2) the methyl ester of 2 : 3-dimethyl methyl-*d*-galacturonoside (0·39 g.), b. p. 160°/0·001 mm. (bath temp.), $n_D^{19°}$ 1·4645, $[\alpha]_D^{20°}$ − 30° (*c*, 1·5 in water) (Found: OMe, 48·1%); (3) 0·1 g. of syrup which partly crystallised, b. p. 175—200°/0·001 mm.

Fraction (2) (0·37 g.) was hydrolysed with N-hydrochloric acid (25 c.c.): $[\alpha]_D^{20°}$ − 30° (initial value); + 47° (1½ hours); + 51° (3·75 hours, constant value). The cooled solution was neutralised with silver carbonate, and filtered before and after the passage of hydrogen sulphide. Evaporation of the solvent gave 2 : 3-dimethyl *d*-galacturonic acid (0·32 g.), $[\alpha]_D^{20°}$ + 35° rising to + 58° in 1 hour (*c*, 6·0 in water) (Found: OMe, 26·9; equiv., 226. Calc. for $C_8H_{14}O_7$: OMe, 27·9%; equiv., 222). The acid (0·30 g.) was dissolved in water (7 c.c.) and oxidised with bromine (1 c.c.) for 12 hours. The solution was then non-reducing. Bromine was removed by aeration and the solution neutralised with silver carbonate and filtered before and after the passage of hydrogen sulphide. Evaporation of the solution gave 2 : 3-dimethyl *d*-mucic acid (0·30 g.) which was converted into the methyl ester of the 1 : 4-lactone of 2 : 3-dimethyl *d*-mucic acid by boiling 3% methyl alcoholic hydrogen chloride (50 c.c., 7 hours). The solution was worked up in the usual manner and the crude ester lactone (0·31 g.) distilled giving the methyl ester of the 1 : 4-lactone of 2 : 3-dimethyl *d*-mucic acid (0·26 g.), b. p. 160°/0·001 mm. (bath temp.), $n_D^{20°}$ 1·4650. The distillate crystallised on nucleation with an authentic specimen of the ester lactone. Trituration with ether and filtration gave crystals (0·20 g.), m. p. and mixed m. p. with an authentic specimen, 96° (Found: OMe, 38·6%).

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229. *Pectic Substances. Part VI. The Structure of the Araban from* Arachis Hypogea.

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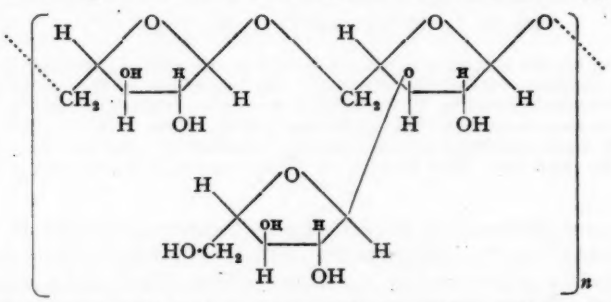
The constitution of the araban component of the pectic material present in the peanut (*Arachis Hypogea*) has been further investigated. On hydrolysis of the methylated araban, trimethyl methyl-*l*-arabofuranoside, 2 : 3-dimethyl methyl-*l*-arabinoside, and a monomethyl methyl-*l*-arabinoside were isolated in the approximate proportions 1 : 1 : 1. The monomethyl arabinose has now been identified as the 2-methyl derivative, and no other monomethyl *l*-arabinose could be detected. The bearing of these results on the structure of araban is discussed.

ARABANS isolated from several sources of pectin have already been examined, and in all cases it has been demonstrated that on hydrolysis the methylated polysaccharide gave rise to three derivatives of arabinose in approximately equal proportions (Hirst and Jones, *J.*, 1938, 496; 1939, 454, 456, 1865). These arabinose derivatives were identified as 2 : 3 : 5-trimethyl *l*-arabofuranose, 2 : 3-dimethyl *l*-arabinose, and a monomethyl *l*-arabinose which was provisionally identified as 3-methyl *l*-arabinose. The identification of this substance was dependent upon the following observations: (1) The sugar had no methoxyl group on C_5, since on acidic hydrolysis of the glycoside it gave a derivative of *l*-arabopyranose characterised by its high positive rotation; (2) it had a hydroxyl group on C_4, since on oxidation it gave a furano-lactone showing a negative rotation and a characteristic slow rate of hydrolysis. Moreover, the rate of hydrolysis of the original araban indicated that all the arabinose components were present in the furanose form and therefore that the hydroxyl group on C_4 was engaged in ring formation and could not be replaced by a methoxyl group after methylation (Hirst and Jones, *J.*, 1939, 454). Only two possibilities, therefore, for the monomethyl derivative remained. It could be either 2- or 3-methyl *l*-arabinose. The latter was thought to be the sugar present in the hydrolysis products of the methylated araban since the amide from the syrupy hydrolysis product gave a positive Weerman test, indicating the presence of an α-hydroxy-amide. It has now been ascertained that this positive test was due to the presence of a small quantity of *l*-arabonamide in the crude syrupy amide, a trace of *l*-arabinose being present in the monomethyl arabinose fraction owing to the difficulty encountered in separating

these two high boiling fractions. In order to obtain further insight into the constitution of the monomethyl arabinose the two sugars, 2- and 3-methyl *l*-arabinose were synthesised and crystalline derivatives of them were prepared (Jones, Kent, and Stacey, in the press; Hirst, Jones, and Williams, in the press). Crystalline derivatives have now been obtained from the monomethyl fraction of the hydrolysis products from methylated araban, and by comparison of these with the synthetic material it has been established beyond doubt that the monomethyl fraction consists almost exclusively of 2-methyl *l*-arabinose (see experimental section). The isolation of the crystalline 2-methyl *l*-arabinose phenylhydrazone, 2-methyl 3 : 4-monoacetone *l*-arabinose, and 2-*methyl* l-*arabonamide* derivatives from the monomethyl fraction was aided by the previous preparation of synthetic crystalline derivatives and by the fact that larger quantities of methylated araban of higher purity were available. This was rendered possible by the observation that araban, which was the major component of the pectin, was methylated much more rapidly than galactan and pectic acid and that the latter can be converted into soluble acid products on heating with 30% sodium hydroxide in the presence of air without destruction of the araban.

With the larger quantities of methylated araban available, it was possible to carry out a rigorous fractionation of the methylated product and thus to obtain a homogeneous product which showed $[\alpha]_D^{20°}$ — 180° in methyl alcohol. It was demonstrated, from observation of the refractive indices and methoxyl values of the fractions obtained on distillation of the products of methanolysis of the methylated araban, that trimethyl, dimethyl, and monomethyl arabinoses are present in equimolecular proportions. The trace of unmethylated arabinose which is also present appears to arise either through incomplete methylation of the polysaccharide or by demethylation of the arabinose fractions during methanolysis.

From these observations the general type of structure present in the araban becomes apparent. The polysaccharide contains only the three residues $A1\ldots.$, $\ldots 5A1\ldots.$, and $\overset{\cdot\cdot}{\cdot\cdot}\overset{3}{5}A1\ldots$ present in equimolecular proportions, A representing an arabofuranose unit linked through the positions indicated. A branched chain structure with terminal arabofuranose residues is clearly present, but the present data do not enable us to differentiate between a main chain of arabofuranose residues composed solely of $\overset{\cdot\cdot}{\cdot\cdot}\overset{5}{\cdot}A1\ldots$ residues and one comprising both this residue and $\ldots.5A1\ldots.$ From rotational data the *l*-arabofuranoside links have the α-configuration, and the general lines of the structure are illustrated in (I) which represents one



(I.)

of the formulæ consonant with the experimental observations, but it is obvious that certain simple variations of this formula are also in agreement with the available experimental evidence. The problem of distinguishing between these requires the development of novel methods of attack, and experimental work is now being undertaken with this object in view. The branched chain of this polymer, which is composed only of *l*-arabofuranose residues, proves that the araban cannot be formed in the plant directly, as a polymer, by simple processes of oxidation and decarboxylation from either the galactan or the pectic acid associated with pectin. The origin and mechanism of the formation of araban remains therefore to be determined.

Experimental.

The seeds (14 kg.) were defatted with benzene and the protein was removed in the usual manner. The residual material was extracted with aqueous potassium hydroxide and crude araban isolated using the conditions described by Hirst and Jones (*loc. cit.*). A portion (50 g.) of the isolated polysaccharides (100 g.) was methylated with sodium hydroxide and methyl sulphate. After two methylations crude methylated araban was isolated by the addition of acetone followed by filtration of the solution to remove insoluble sodium salts and polysaccharide material. After the insoluble methylated material had been separated the aqueous solution was acidified and extracted with chloroform. Concentration of the extract gave some methylated pectic acid (4 g.), $[\alpha]_D^{18°}$ + 114° (*c*, 0·57 in methyl alcohol) (Found: OMe,

38%). The filtered acetone solution on evaporation gave a pale yellow sticky solid which was further methylated by use of Purdie's reagents. The polysaccharide (35 g.) was fractionated from chloroform (100 c.c.) by the gradual addition of light petroleum (b. p. 40—60°), giving:

Fraction A (0·9 g.), mainly inorganic material.
Fraction B (6·2 g.), $[\alpha]_D^{25°}$ − 144° (*c*, 1·1 in methyl alcohol) (Found: OMe, 38·7%).
Fraction C (15 g.), $[\alpha]_D^{25°}$ − 176° (*c*, 1·3 in methyl alcohol) (Found: OMe, 38·3%).
Fraction D (8·1 g.), $[\alpha]_D^{25°}$ − 180° (*c*, 0·7 in methyl alcohol) (Found: OMe, 38·0%).
Fraction E (4·0 g.), $[\alpha]_D^{25°}$ − 179° (*c*, 0·9 in methyl alcohol) (Found: OMe, 38·0%).

All these fractions were pale yellow sticky solids. The residue (1·0 g.) was discarded.

Trial Hydrolysis.—Fraction D (7·9 g.) was dissolved in methyl alcohol (75 c.c.)–water (25 c.c.) containing oxalic acid dihydrate (0·1 g.) and boiled under reflux in an attempt to bring about a graded hydrolysis of the polysaccharide (see Hirst and Young, *J.*, 1939, 1480). The optical rotation (− 184°) remained constant and no hydrolysis occurred during 20 hours under these conditions even when the oxalic acid concentration was raised to 0·5 g./100 c.c. Accordingly, oxalic acid was removed by neutralisation with calcium carbonate and the unchanged polysaccharide submitted to hydrolysis with boiling methyl alcohol (100 c.c.) containing hydrogen chloride (2 g.) for 30 hours. Change of optical rotation could not be observed owing to darkening of the solution. The cooled solution was neutralised by cautious addition of ethereal diazomethane and the solvents were removed at 60°. The residual syrup (9·4 g.) was then fractionated by continuous extraction from aqueous solution (Z) with light petroleum (b. p. 40—60°) giving an extract—*Fraction* 1 (2·89 g.), $n_D^{19°}$ 1·4360—which was distilled yielding *Fraction* 1*a* (2·54 g.), b. p. 130°/12 mm., $n_D^{18°}$ 1·4352 (Found: OMe, 60·0%), and a still residue (0·28 g.). The aqueous solution (Z, above) was then extracted continuously with ether and the extracts concentrated at 40° to a syrup—*Fraction* 2 (3·68 g.)—which was added to the still residue (0·28 g. above) and the whole fractionally distilled giving *Fraction* 2*a* (1·3 g.), b. p. 120°/0·2 mm., $n_D^{22°}$ 1·4452 (Found: OMe, 52·3%); *Fraction* 2*b* (1·87 g.), b. p. 125°/0·01 mm., $n_D^{21°}$ 1·4487 (Found: OMe, 47·8. Calc. for $C_8H_{16}O_5$: OMe, 48·4%); still residue (S, 0·62 g.). The aqueous solution (Z) after extraction with light petroleum and ether was evaporated in a vacuum to a syrup which was combined with the still residue (S, 0·62 g.) and the mixture (2·8 g.) distilled under reduced pressure giving *Fraction* 3*a* (0·25 g.), b. p. 125°/0·01 mm., $n_D^{22°}$ 1·4582 (Found: OMe, 43·7%); *Fraction* 3*b* (1·06 g.), b. p. 125°/0·01 mm., $n_D^{23°}$ 1·4662 (Found: OMe, 42·2%); *Fraction* 3*c* (0·68 g.), b. p. 125°/0·01 mm., $n_D^{23°}$ 1·4750 (Found: OMe, 24·8%), and a still residue (0·76 g.) (Found: OMe, 25·1%).

Fraction 1a on hydrolysis gave 2 : 3 : 5-trimethyl *l*-arabofuranose in quantitative yield, $[\alpha]_D^{20°}$ − 38° (in water), identified by conversion into the crystalline lactone, m. p. 29°, of 2 : 3 : 5-trimethyl *l*-arabonolactone and into 2 : 3 : 5-trimethyl *l*-arabonamide, m. p. 139°. Fraction 2a was a mixture of the methyl glycosides of 2 : 3 : 5-trimethyl *l*-arabofuranose and 2 : 3-dimethyl *l*-arabinose since it was separated into 2 : 3 : 5-trimethyl methyl-*l*-arabinoside (0·90 g.), identified as crystalline 2 : 3 : 5-trimethyl *l*-arabonolactone, m. p. 29°—prepared in the usual manner—and 2 : 3-dimethyl methyl-*l*-arabinoside (0·35 g.), $n_D^{22°}$ 1·4454, on fractional extraction from aqueous solution with light petroleum (b. p. 40—60°). This last fraction was combined with Fraction 2b and the whole (2·1 g.) hydrolysed with N-hydrochloric acid at 100°; $[\alpha]_D^{20°}$ − 35° ⟶ $[\alpha]_D^{20°}$ + 92° (constant value). The resultant syrup (1·9 g.) ($[\alpha]_D^{18°}$ + 104°, *c*, 1·1 in water) (Found: OMe, 34·4. Calc. for $C_7H_{14}O_5$: OMe, 34·6%), isolated in the usual manner, was mainly if not entirely 2 : 3-dimethyl *l*-arabinose since it gave, in good yield, the corresponding 2 : 3-dimethyl anilino-*l*-arabinose, m. p. and mixed m. p. 139°. On refluxing it with alcoholic aniline, no other derivative of arabinose could be detected.

Fractions 3a and 3b were combined (1·80 g.) and separated by fractional extraction from water with ether into 2 : 3-dimethyl methyl-*l*-arabinoside (0·8 g.), identified, after hydrolysis to 2 : 3-dimethyl *l*-arabinose with N-hydrochloric acid, as 2 : 3-dimethyl anilino-*l*-arabinose, m. p. and mixed m. p. 139°. The more water-soluble fraction (1·0 g.) was 2-monomethyl methyl-*l*-arabinoside which was combined with Fraction 3c and the whole (1·65 g.) hydrolysed with boiling N-sulphuric acid (25 c.c.); $[\alpha]_D^{20°}$ + 81° (constant value) ⟶ + 94° (constant value after 6 hours). The residual syrup (1·3 g.) did not crystallise (Found: OMe, 19·4. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). A sample, on refluxing with alcoholic phenylhydrazine, gave 2-methyl *l*-arabinose phenylhydrazone, m. p. and mixed m. p. 115° (see below). On shaking a sample of the syrup with acetone and anhydrous copper sulphate, 2-methyl monoacetone *l*-arabinose was formed in quantitative yield, m. p. and mixed m. p. 117° (Found: C, 52·7; H, 7·8; OMe, 15·2. Calc. for $C_9H_{16}O_5$: C, 52·9; H, 7·8; OMe, 15·2%).

A portion (0·66 g.) of the still residue was hydrolysed with hot N-sulphuric acid (18 c.c.). The syrup (0·56 g.), $[\alpha]_D$ + 92° (Found: OMe, 17·4%), isolated in the usual manner was almost entirely 2-methyl *l*-arabinose since it gave the corresponding crystalline phenylhydrazone, m. p. and mixed m. p. 115°, on refluxing with an alcoholic solution of phenylhydrazine. Some *l*-arabinose was also present since the syrup gave, in small yield with an alcoholic solution of benzoylhydrazine, a precipitate of *l*-arabinose benzoylhydrazone, m. p. 184°.

Large Scale Hydrolysis of Methylated Araban.—Fraction C (14·46 g.) was hydrolysed by boiling with methanolic hydrogen chloride (100 c.c.; 1%) for 12 hours. Changes in optical rotation were not observable owing to darkening of the solution. The cooled solution was neutralised with a slight excess of diazomethane in ether and the solvents were removed as quickly as possible at 70°. The syrupy residue (17·1 g.) was then dissolved in water (50 c.c.) and extracted continuously for 24 hours in an all-glass apparatus with light petroleum (sulphur-free, b. p. 35—37°). After removal of the solvent at 40° there remained a syrup (7·05 g., $n_D^{22°}$ 1·4388). The aqueous solution was then extracted continuously for a further 24 hours with ether. Concentration of the extracts gave a syrup (4·75 g.). The residual aqueous solution on removal of water gave a syrup (5·2 g.) which was extracted with chloroform, giving a syrup (5·0 g.) soluble in chloroform and leaving crystalline β-methyl-*l*-arabopyranoside (0·2 g.), m. p. 164—168° not depressed on admixture with an authentic specimen.

Fractional Distillation of the Syrups.—The light-petroleum-soluble syrup (7·05 g., $n_D^{22°}$ 1·4388) was

distilled at 20 mm., giving: *Fraction* 4 (4·94 g.), b. p. 145° (bath temp.), $n_D^{21°}$ 1·4359 (Found: OMe, 59·2. Calc. for $C_9H_{18}O_5$: OMe, 60·2%); *Fraction* 5 (1·46 g.), b. p. 155°, $n_D^{21°}$ 1·4432 (Found: OMe, 54·0. Calc. for $C_8H_{16}O_5$: OMe, 48·4%). The still residue (0·69 g.) was added to the ethereal extract (4·75 g.) and the whole distilled at 0·01 mm. giving *Fraction* 6 (2·34 g.), b. p. 110° (bath temp.), $n_D^{22°}$ 1·4515 (Found: OMe, 48·4. Calc. for $C_8H_{16}O_5$: OMe, 48·4%). The syrup soluble in chloroform (5 g., see above) was added at this stage and the distillation continued. *Fraction* 7 (2·55 g.), b. p. 140° (bath temp.), $n_D^{24°}$ 1·4565 (Found: OMe, 48·1. Calc. for $C_8H_{16}O_5$: OMe, 48·4%); *Fraction* 8 (2·11 g.), b. p. 155° (bath temp.), $n_D^{24°}$ 1·4672 (Found: OMe, 40·3. Calc. for $C_7H_{14}O_5$: OMe, 34·8%); *Fraction* 9 (1·06 g.), b. p. 160° (bath temp.), $n_D^{20°}$ 1·4715 (Found: OMe, 34·9. Calc. for $C_7H_{14}O_5$: OMe, 34·8%); *Fraction* 10 (0·65 g.), b. p. 190° (bath temp.), $n_D^{20°}$ 1·4745 (Found: OMe, 32·1. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). The still residue (1·20 g.) (Found: OMe, 30·5%) was methylated with Purdie's reagents (see below).

Examination of the Fractions.—A portion of Fraction 4 (4·84 g.) was dissolved in N-sulphuric acid (25 c.c.) and hydrolysed at 90° for 3½ hours; $[\alpha]_D^{20°}$ − 86° ⟶ − 30° (constant value). The sugar (4·5 g.) was isolated by continuous extraction of the solution with chloroform (Found: OMe, 48·0. Calc. for $C_8H_{16}O_5$: OMe, 48·4%). The sugar was converted into 2 : 3 : 5-trimethyl *l*-arabonolactone by the following general method. The sugar (4·5 g.) was dissolved in N-sodium hydroxide (150 c.c.), and iodine (12 g.) added. After 12 hours, excess of iodine was removed with sulphur dioxide and the solution then acidified with sulphuric acid and extracted continuously with chloroform. Concentration of the chloroform extract gave a syrup (4·3 g.), $n_D^{20°}$ 1·4448, which crystallised on nucleation with 2 : 3 : 5-trimethyl *l*-arabonolactone, m. p. and mixed m. p. with an authentic specimen, 28°. This fraction therefore consists entirely of 2 : 3 : 5-trimethyl methyl-*l*-arabinoside.

Fraction 5 (1·45 g.) was dissolved in N-sulphuric acid (25 c.c.) and hydrolysed on the steam-bath; $[\alpha]_D^{20°}$ − 81° ⟶ $[\alpha]_D^{20°}$ + 30° (final value). The free sugars (1·35 g.) isolated in the usual manner (Found: OMe, 41·8%) were oxidised with bromine (2 c.c.) in water (5 c.c.) for 12 hours. The lactones—isolated by chloroform extraction of the solution after removal of excess of bromine—were distilled in a vacuum giving impure 2 : 3 : 5-trimethyl *l*-arabonolactone (0·7 g.), m. p. 20°, and impure 2 : 3-dimethyl *l*-arabofuranolactone, b. p. 130° (bath temp.)/0·4 mm., $n_D^{21°}$ 1·4578. The lactones gave, with alcoholic ammonia, the corresponding crystalline amides, *viz.*, 2 : 3 : 5-trimethyl *l*-arabonamide, m. p. 138°, and 2 : 3-dimethyl-*l*-arabonamide, m. p. 161°. It is inferred that this fraction consists of 2 : 3 : 5-trimethyl and 2 : 3-dimethyl methyl-*l*-arabinoside in approximately equal proportion.

Fraction 6 (2·22 g.) was hydrolysed by boiling with N-sulphuric acid (20 c.c.) for 3 hours; $[\alpha]_D^{20°}$ − 51° ⟶ + 101° (constant value). The resultant 2 : 3-dimethyl *l*-arabinose (2·0 g.) was isolated by exhaustive chloroform extraction of the solution after neutralisation with N-sodium hydroxide. Since this fraction showed an inversion of sign the material was 2 : 3-dimethyl methyl-*l*-arabinoside mainly in the furanose form.

Fraction 7 (2·42 g.) was dissolved in N-sulphuric acid and hydrolysed by heating the solution to 90°; $[\alpha]_D^{20°}$ + 56° ⟶ + 102° (constant value). The syrupy sugar was isolated from the neutralised solution by exhaustive chloroform extraction (yield, 2·2 g.). This fraction was 2 : 3-dimethyl methyl-*l*-arabinoside mainly in the pyranose form.

The sugars from Fractions 6 and 7 were combined (4·2 g.), $[\alpha]_D^{20°}$ + 104° (*c*, 1·3 in water) (Found: OMe, 34·6. Calc. for $C_7H_{14}O_5$: OMe, 34·8%), and oxidised by dissolving in water (10 c.c.) containing bromine (5 c.c.). The solution became hot and was left for 12 hours. Bromine was then removed, first by aeration, and then by passage of sulphur dioxide. The solution was then extracted exhaustively with chloroform and the resultant 2 : 3-dimethyl *l*-arabofuranolactone (4·1 g.) purified by distillation in a vacuum; b. p. 140° (bath temp.)/0·5 mm., $n_D^{24°}$ 1·4575. With alcoholic ammonia the lactone gave 2 : 3-dimethyl *l*-arabonamide, m. p. 162°, in quantitative yield.

Fraction 8 was a mixture of 2 : 3-dimethyl methyl-*l*-arabinoside and 2-methyl methyl-*l*-arabinoside. Partial separation of the components was achieved by the following method. The glycosides (2·0 g.) were dissolved in acetone (25 c.c.) containing hydrogen chloride (1 g.) (see Hirst and Jones, *J.*, 1939, 456). After 20 hours the solution was poured into an aqueous solution of sodium hydrogen carbonate and the neutral solution extracted with chloroform. The extracts were dried (K_2CO_3), filtered, and concentrated to a syrup (1·74 g.) which was distilled under reduced pressure giving a first fraction, b. p. 106° (bath temp.)/0·5 mm. (0·6 g.), $n_D^{20°}$ 1·4500 (Found: OMe, 30·0. Calc. for 2-methyl monoacetone methyl-*l*-arabinoside: OMe, 28·4%), and a second fraction, b. p. 120°/0·5 mm. (0·8 g.), $n_D^{20°}$ 1·4610 (Found: OMe, 43·0. Calc. for 2 : 3-dimethyl methyl-*l*-arabinoside: OMe, 48·4%). The still residue was mainly 2-methyl methyl-*l*-arabinoside (Found: OMe, 36·0. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). The impure 2-methyl monoacetone methyl-*l*-arabinoside (0·5 g.) was hydrolysed with boiling N-sulphuric acid, $[\alpha]_D^{20°}$ + 100° (final value), and the sugar (0·3 g.) isolated in the usual manner. It was identified, after boiling with alcoholic phenylhydrazine, as 2-methyl *l*-arabinose phenylhydrazone, m. p. and mixed m. p. 115°. This same derivative was isolated after boiling the free sugar, obtained from the hydrolysis of the still residue with hot N-sulphuric acid, with alcoholic phenylhydrazine. The second fraction (above) on hydrolysis with boiling N-sulphuric acid (20 c.c.) gave 2 : 3-dimethyl *l*-arabinose which was identified as its anilide, obtained by boiling an alcoholic solution of the sugar with aniline, m. p. 138° not depressed on admixture with an authentic specimen.

Fractions 9 and 10 consisted of 2-methyl methyl-*l*-arabinoside. These fractions were combined and the syrup (1·65 g.) hydrolysed with boiling N-sulphuric acid (20 c.c.); $[\alpha]_D^{20°}$ + 104° (final value; initial value not observable). The free sugar (1·5 g.) was isolated after neutralisation of the solution with barium carbonate followed by filtration and concentration under reduced pressure (Found: OMe, 18·7. Calc. for $C_6H_{12}O_5$: OMe, 18·9%).

A portion of the syrup (0·1 g.) on heating with alcoholic phenylhydrazine gave 2-methyl *l*-arabinose phenylhydrazone (0·1 g.), m. p. 115° not depressed on admixture with an authentic specimen. The syrup (0·4 g.) was oxidised with bromine (1 c.c.) in water (5 c.c.) at 30° for 12 hours. Bromine was removed by aeration and the 2-methyl *l*-arabonolactone isolated by exhaustive extraction of the solution

with chloroform. The lactone (0·35 g.) did not crystallise, but with an alcoholic solution of ammonia it gave *2-methyl* l-*arabonamide* (0·3 g.), $[\alpha]_D$ + 51° (*c*, 1·1 in water), m. p. 130° depressed to 124° on admixture with 3-methyl *l*-arabonamide, m. p. 131° (Found: C, 40·1; H, 7·4; N, 7·8; OMe, 17·2. $C_6H_{13}O_5N$ requires C, 40·2; H, 7·3; N, 7·8; OMe, 17·3%). 2-Methyl *d*-arabonamide has $[\alpha]_D$ − 53° (in water), m. p. 131° (Schmidt and Simon, *J. pr. Chem.*, 1942, **152**, 199).

To prove the absence of any quantity of 3-methyl *l*-arabinose, the following procedure was adopted. The syrupy sugar (1·0 g.) was boiled with 3% methyl-alcoholic hydrogen chloride for 24 hours to ensure a maximum conversion into the pyranoside derivative. The solution was neutralised with silver carbonate and filtered, and the residual non-reducing syrup (0·92 g.), $[\alpha]_D^{20°}$ + 143° (*c*, 0·9 in water), was dissolved in water and oxidised with excess of sodium periodate solution (30 c.c.; 0·3M) for 24 hours. The aqueous solution was then extracted, first with ether, which is known to extract monomethyl methyl-*l*-arabinoside very slowly indeed, and then with chloroform. Concentration of the ethereal extract gave a mobile reducing syrup (0·7 g.) from which no identifiable product could be isolated. The chloroform extract on concentration gave a sticky brown solid (0·2 g.), which on hydrolysis with N-sulphuric acid was completely decomposed with the formation of resinous products. No 3-methyl *l*-arabinose, which would not have been oxidised with sodium periodate, could be detected, nor could any derivative of 3-methyl *l*-arabinose be isolated. It is concluded that any appreciable quantity of 3-methyl *l*-arabinose is absent from the products of hydrolysis of methylated araban.

The still residue (1·2 g.) was methylated with silver oxide and methyl iodide (twice) and the syrupy sugar distilled in a vacuum giving a mobile syrup (0·9 g.), $n_D^{20°}$ 1·4480 (Found: OMe, 59·1%), which on hydrolysis with boiling N-sulphuric acid gave 2 : 3 : 4-trimethyl *l*-arabinose, $n_D^{20°}$ 1·4540, $[\alpha]_D^{20°}$ + 112° (*c*, 1·1 in water) (Found: OMe, 46·0%).

On oxidation with bromine water the syrup (0·4 g.) gave the corresponding δ-lactone, isolated as the crystalline amide, m. p. 95° (Found: OMe, 44·2. Calc. for $C_8H_{17}O_5N$: OMe, 44·9%).

From an examination of the various fractions, it may be calculated from the values of refractive index and methoxyl of each fraction that the sugars 2 : 3 : 5-trimethyl *l*-arabinose, 2 : 3-dimethyl *l*-arabinose, and 2-methyl *l*-arabinose are present in a ratio approximating very closely to 1 : 1 : 1.

THE UNIVERSITY, MANCHESTER. [*Received, November 28th*, 1946.]

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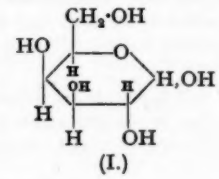
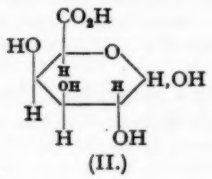
230. *Pectic Substances. Part VII. The Constitution of the Galactan from* Lupinus albus.

By E. L. HIRST, J. K. N. JONES, and (MRS.) W. O. WALDER.

A galactan has been isolated from the pectin component of *Lupinus albus*. This polysaccharide is a linear polymer built up of *d*-galactose residues which, after methylation followed by hydrolysis, yields 2 : 3 : 6-trimethyl *d*-galactose together with a small amount of 2 : 3 : 4 : 6-tetramethyl *d*-galactose from the end group. The amount of this latter sugar corresponds to an average repeating unit of approximately 100 galactose residues. The isolation of this polysaccharide is further evidence that galactan is not converted into araban by a simple process of oxidation followed by decarboxylation of the resultant uronic acid residue.

MOST samples of pectin on hydrolysis furnish a mixture of the three sugars *d*-galactose (I), *d*-galacturonic acid (II), and *l*-arabinose (III), and at one time it was considered possible that pectin was a single substance which possessed a cyclic structure built up from these residues. Ehrlich, however, demonstrated that pectin contained an araban as a separate entity, and subsequent work has indicated that at any rate most of the arabinose encountered in pectic


(I.)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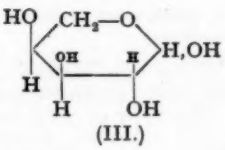
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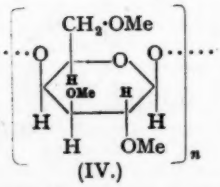
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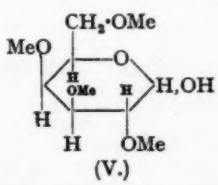
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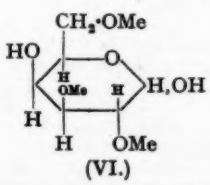
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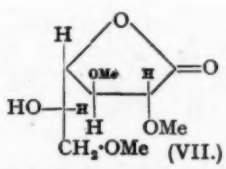

(VII.)

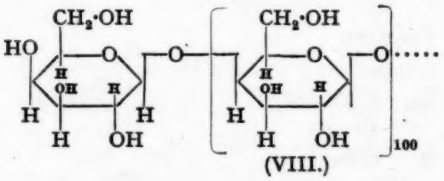
materials is present in the form of this araban component. It seemed probable that the galactose residues also might be present as a separate polysaccharide, and it is shown in the

present communication that the pectic material of the seeds of the white lupin does in fact contain a galactan, which can be separated from the pectic acid and the araban components. Since the conversion of (I) into (III) may proceed in Nature through (II), which then undergoes decarboxylation, it was of considerable interest to examine in detail the constitution of this galactan and to determine whether it was unbranched, as in pectic acid, or branched, as in araban, and thus to decide whether it could be structurally related to either the pectic acid or the araban component of pectin. In the former case the sugar residues should be of the pyranose form and linked through α-linkages, whilst in the latter case the *d*-galactose residues should be of the furanose form.

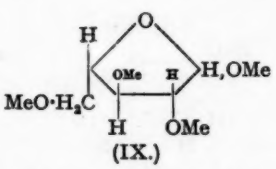
In common with many other plant materials the seed of the white lupin contains material which on hydrolysis is converted into *d*-galactose and *l*-arabinose (" The Principles of Plant Biochemistry ", M. W. Onslow, Cambridge University Press, 1931 Edtn., p. 72). Professor M. Skene of the University of Bristol had informed us that these seeds were a particularly rich source of pectin, and we investigated their carbohydrate content with the object of isolating the galactan component. We found that the carbohydrate fraction of the seed contained a pectin-like material in which the percentage of uronic acid component and of araban was much lower than any other sample of pectin we had hitherto encountered, and thus enabled us to obtain, in a relatively easy manner, a sample of the galactan. Associated with this galactan there was an araban which could be partly removed by extraction with 70% alcohol and a pectic acid which could be precipitated as calcium pectate. The araban showed the same ease of hydrolysis and high negative rotation as the araban associated with apple, citrus, and peanut pectins. The pectic acid component could be converted into a degraded product (see Morrel, Baur, and Link, *J. Biol. Chem.*, **1934**, **105**, 1) which had properties close to those of the corresponding polysaccharides from apple and citrus pectins.

It was inferred, therefore, that we were dealing with a true pectin which was, however, particularly rich in galactan. This galactan, which could not be obtained completely free from adsorbed araban and pectic acid, had $[\alpha]_D$ + 38° in water. This value is low since the material still contained some 19% of pentosan and the corrected figure is therefore more likely to be about + 70°. After methylation with thallium hydroxide and methyl iodide (Menzies, *J.*, **1926**, 937; Hirst and Jones, *J.*, **1938**, 496) a methylated product was isolated which contained methylated araban and methylated galactan. The small quantity of pectic acid present was very difficult to methylate and was lost during the process (Hirst and Jones, *loc. cit.*). Methylated araban was separated from methylated galactan by extraction of the former from the mixture with ether. The ether-insoluble material had $[\alpha]_D^{20°}$ − 12° in methyl alcohol, this negative value being an indication that in methylated galactan the sugar residues are joined together by β-linkages and that the galactan cannot be directly related to pectic acid in which the sugar residues are joined together by α-linkages. Methylated galactan (IV) was resistant to hydrolysis and the rate of reaction corresponded to that of a typical galactopyranoside. Fractional distillation of the sugars formed on methanolysis of the methylated galactan led to the identification of tetramethyl *d*-galactopyranose (V), isolated as its crystalline anilide, and **2 : 3 : 6**-trimethyl *d*-galactose (VI), identified after oxidation as its crystalline furanolactone (VII). The inferences are, therefore, that the galactan is built up of *d*-galactopyranose residues linked through carbon atoms 1 and 4 and that the molecule is linear. The optical rotatory power of the galactan points to the occurrence of β-galactosido-linkages, and the amount of tetramethyl galactose isolated suggests that there is approximately one end group per 100 galactose residues.

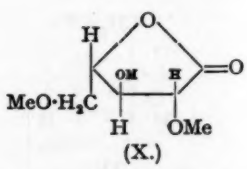
In the absence of evidence concerning molecular weight it is not possible at present to say whether this figure represents the molecular size or the size of the repeating unit in a larger molecule. The type of structure present is shown in (VIII). The methylated araban could



(VIII.)



(IX.)



(X.)

not be obtained in a pure state, and a complete examination of it could not be attempted. Nevertheless, methanolysis of the crude material, which still contained much galactan, gave some **2 : 3 : 5**-trimethyl methyl-*l*-arabinoside (IX) identified as crystalline **2 : 3 : 5**-trimethyl

l-arabonolactone (X), the identity of which was confirmed by conversion into the corresponding crystalline amide. These arabofuranose residues were therefore terminal groups of the type previously found to be present in arabans associated with other pectic materials.

It is clear from these results that the araban cannot be formed directly from this galactan by processes of oxidation and decarboxylation at position 6. If phytochemical changes of this type do occur it would be necessary to postulate the participation of three types of galactan and two types of pectic acid in the reactions concerned (cf. Hirst, *J.*, 1942, 70). No evidence for the presence of isomeric pectic acids and galactans in pectic materials has yet been obtained, and it would appear much more likely that the various polysaccharides are formed by separate synthetic reactions. In addition, there remains the problem, still quite unsolved, as to whether the plant can utilise the *d*-galactose residues present in the galactan and convert them after hydrolysis into pectic acid and araban, or whether the synthesis proceeds from material other than *d*-galactose. On the basis of present knowledge the possibility cannot be ruled out that the simultaneous occurrence of the three stereochemically closely related substances *d*-galactose, *d*-galacturonic acid, and *l*-arabinose may have no immediate phytochemical significance.

Experimental.

Extraction of the Polysaccharides from the Seeds of Lupinus albus.—After being soaked overnight in water, the seeds were stripped of their skins and milled twice. The protein matter was then extracted by stirring the finely ground material with aqueous sodium chloride solution (10%) for 3 hours, followed by filtration and repetition of the process thrice. The solid residue was then stirred with aqueous sodium hydroxide (0·2%) thrice for 12 hours at a time. Addition of hydrochloric acid to the filtrate then gave no precipitate, indicating the absence of any appreciable quantities of protein. The solid residue was then boiled with aqueous sodium hydroxide (0·2%) for 3 hours, after which it was filtered and the filtrate poured into methylated spirit (4 vols.). The precipitated polysaccharide was filtered off, washed with alcohol, and dried in a vacuum at 90°. The resulting product was extracted with water, the solution was centrifuged to separate insoluble material, and the polysaccharide was precipitated by addition of methylated spirit acidified with hydrochloric acid. The precipitate was then filtered off, washed until free from acid, and dried in a vacuum at 90°. The product (*A*) was a non-reducing cream-coloured powder. Yield, 4%. $[\alpha]_D^{20°}$ + 52° (as sodium salt in water) [Found: furfuraldehyde, 26·5; uronic anhydride, 8% (corresponding to an equiv. of 2200 and 2% of the total furfuraldehyde); N, nil; OMe, nil; equiv., 1430 (by titration with 0·1N-sodium hydroxide)].

Hydrolysis of the Polysaccharide Material (A).—This material (15 g.) was boiled with N-sulphuric acid (250 c.c.) for 6 hours. Hydrolysis was then complete since the optical rotation and reducing power had become constant. A small quantity of flocculent material (0·8 g.) was removed on the centrifuge and the solution was neutralised with barium carbonate and filtered. The filtrate was concentrated under reduced pressure at 40° and poured into methyl alcohol (50 c.c.), and the precipitated barium salts were removed by filtration. The filtrate from the barium salts was concentrated under reduced pressure to a syrup which crystallised. The crystalline solid, m. p. 157° (3·6 g.), separated by filtration after trituration with methyl alcohol, was *d*-galactose since it gave mucic acid, m. p. 210°, after oxidation with nitric acid, and with methylphenylhydrazine it gave the phenylmethylhydrazone, m. p. and mixed m. p. with an authentic sample 186°.

After removal of crystalline galactose the filtrate was concentrated to a syrup and made up to 250 c.c. with water. An iodometric titration at this stage showed that the solution contained 10·3 g. of sugar calculated as hexose, or 8·6 g. calculated as pentose. Furfuraldehyde determinations on the solution indicated that pentose (3·9 g.) was present. Confirmation of this figure was obtained by determination of arabinose as its diphenylhydrazone by the method of Wise and Peterson (*Ind. Eng. Chem.*, 1930, **22**, 362). This determination indicated the presence of arabinose (3·9 g.). Other pentoses, except in traces, were therefore absent. Determination of galactose by the mucic acid method as modified by Wise and Peterson (*loc. cit.*) indicated the presence of galactose (6·1 g.). These figures for arabinose (3·9 g.) and for galactose (6·1 g.) are in agreement with the total sugar content obtained by iodometric titration and show that (*A*) contains approximately 6% of galactose residues and 26% of arabinose residues. Some pectic acid is also present.

(*A*) (100 g.) was shaken with 70% methyl alcohol (2½ l.) for 3 months. The slurry was then centrifuged and the supernatant liquid evaporated to dryness. The residual solid (0·1 g.) had $[\alpha]_D^{20°}$ − 119° (*c*, 1·0 in water) and yielded 32% of furfuraldehyde on distillation with 12% hydrochloric acid, corresponding to the presence of 64% of pentose.

Since (*A*) was possibly a mixture of an araban and galactan, a portion of it (3 g.) was boiled with 0·01N-oxalic acid at 100° until the optical rotation was constant. A small amount of insoluble material which separated appeared to be impure pectic acid; it had $[\alpha]_D^{20°}$ + 157° (in water) (Found: equiv., 370). The solution was filtered before and after neutralisation with calcium carbonate, and concentrated to dryness. The residual solid was extracted with methyl alcohol and the solution filtered and concentrated to a syrup (0·285 g.) which had $[\alpha]_D^{20°}$ + 91° in water and contained 36% of pentosan (calculated from the yield of furfuraldehyde obtained on distillation with 12% hydrochloric acid). The methyl alcohol-insoluble solid (2·0 g.) gave a negative test for pentoses and had $[\alpha]_D^{20°}$ + 77° in water. On hydrolysis with 1% sulphuric acid it gave *d*-galactose, m. p. and mixed m. p. 158°. The phenylmethylhydrazone had m. p. 184°. No other sugar could be detected.

Purification of (A) *by removal of calcium pectate.* Crude (*A*) contained some uronic acid (see above) which was largely removed in the following manner. The polysaccharide (80 g.) was dissolved in cold water and neutralised with 0·1N-sodium hydroxide, and calcium chloride solution was added to

precipitate the polyuronide as its calcium salt. The insoluble material was then removed on the centrifuge and the water soluble polysaccharide mixture (*B*) was precipitated by addition of alcohol (5 vols.); $[\alpha]_D^{20°}$ + 38° in water (Found: uronic anhydride, 2%; furfuraldehyde, 9·6%; equiv., 3060).

All attempts to separate completely the pentosan, galactan, and uronic acid fractions of (*A*) either by acid treatment or by fractional precipitation were unsuccessful. Accordingly, (*B*) (15 g.) was methylated by the standard thallous hydroxide–methyl iodide procedure (Menzies, *loc. cit.*; Hirst and Jones, *loc. cit.*). The methylation was completed by boiling with methyl iodide and silver oxide. The product (12 g.) (Found: OMe, 42%) was isolated in the usual manner.

Fractionation. The methylated product (12 g.) was dissolved in chloroform (50 c.c.) and fractionated by the portionwise addition of light petroleum (b. p. 40—60°). By this means the following fractions were obtained: Fraction I (0·9 g.), $[\alpha]_D^{20°}$ − 16° in methyl alcohol (Found: OMe, 40·3%). Fraction II (8·1 g.), $[\alpha]_D^{20°}$ − 12° in methyl alcohol [Found: furfuraldehyde (on boiling with 12% hydrochloric acid, see Bott and Hirst, *J.*, 1932, 2621), 3·1; OMe, 39·1%]. Fraction III (2 g.), $[\alpha]_D^{20°}$ − 12° in methyl alcohol (Found: OMe, 39·9%). Fraction IV (0·5 g.), $[\alpha]_D^{20°}$ − 13° in methyl alcohol (Found: OMe, 39·2%). Fraction V (0·4 g.), $[\alpha]_D^{20°}$ − 15° in methyl alcohol (Found: furfuraldehyde, 9·5; OMe, 37·5%).

Fractions I, II, III, and IV were combined and re-methylated with silver oxide and methyl iodide since their methoxyl content was still low. The product, isolated in the usual manner, was separated into two fractions by extraction with boiling methyl iodide. This separation of the methylated polysaccharide into methyl iodide-soluble and -insoluble fractions indicated that there was a substantial difference in the physical properties of the two components. The analytical figures and optical rotations, however, showed little difference between the two fractions. This was confirmed on examination of the products of methanolysis of the two fractions (see below). The solubility difference observed is due probably to difference in molecular weight and not to a substantial difference in chemical constitution. No pentose could be detected in the products of hydrolysis of either fraction.

The methyl iodide-soluble material (4·0 g.) had $[\alpha]_D^{20°}$ − 15·7° in methyl alcohol (Found: C, 51·0; H, 7·7; OMe, 39·5%). No acidic groups (uronic acids) were present. The methyl iodide-insoluble material (7·4 g.) had $[\alpha]_D^{20°}$ − 17° in methyl alcohol (Found: C, 51·6; H, 7·9; OMe, 41·6%). No acid groups (uronic acids) were present.

Hydrolysis of the Fraction Soluble in Methyl Iodide.—This polysaccharide derivative was very resistant to methanolysis even on prolonged boiling with fairly high concentrations of hydrogen chloride. Accordingly the methylated polysaccharide (3·9 g.) was dissolved in a solution (50 c.c.) containing glacial acetic acid (2 vols.), concentrated hydrochloric acid (1 vol.), and water (1 vol.) and heated on a water-bath until the rotation was constant (8 hours). The solution was partially neutralised with barium carbonate (to remove all the hydrochloric acid) and filtered, and the filtrate and washings were evaporated to dryness under reduced pressure to remove acetic acid and water. The solid residue was extracted exhaustively with chloroform and the extracts were concentrated under reduced pressure and converted into the methyl glycosides by boiling with methyl alcoholic hydrogen chloride (3%, 7 hours). The resulting methyl glycosides (3·9 g.) were isolated and fractionally distilled giving: Fraction 1 (0·30 g.), b. p. 129°/0·001 mm., $n_D^{20°}$ 1·4495 (Found: OMe, 54·1%). Fraction 2 (2·45 g.), b. p. 140—160°/0·001 mm., $n_D^{20°}$ 1·4568 (Found: OMe, 50·7%). Fraction 3 (0·38 g.), b. p. 160—175°/0·001 mm., $n_D^{20°}$ 1·4560 (Found: OMe, 50·6. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). Fraction 4 (0·33 g.), b. p. 175—240°/0·001 mm., $n_D^{20°}$ 1·4686 (Found: OMe, 41·4%). Still residue (0·44 g.), not further examined.

Examination of the fractions. Fractions 1 and 2 (2·7 g.) were combined and hydrolysed with N-hydrochloric acid (20 c.c.) at 90—95°. $[\alpha]_D^{20°}$ + 20° (initial value) ⟶ + 81° (3 hours, constant value). The solution was cooled, neutralised with barium carbonate, filtered, and concentrated under reduced pressure to a solid which was exhaustively extracted with chloroform. On concentration the extracts gave a syrup (2·4 g.); $n_D^{21°}$ 1·4772; $[\alpha]_D^{20°}$ + 37° (in methyl alcohol) (Found: OMe, 40·9. Calc. for $C_9H_{18}O_6$: OMe, 41·8%). A sample of the syrup (0·039 g.) on dissolving in 3% methyl alcoholic hydrogen chloride (5 c.c.) showed a change of optical rotation identical with that given by 2 : 3 : 6-trimethyl *d*-galactose. $[\alpha]_D^{20°}$ + 36° (initial value); + 8° (8¼ hours); + 0° (14 hours); − 16° (20 hours); − 26° (36 hours, constant value). The sugar (0·89 g.) was dissolved in water (5 c.c.) and bromine (1·5 c.c.) added. The solution was heated to 55° for 4 hours; a test sample after aeration to remove bromine then showed no reduction when heated with Fehling's solution. Bromine and hydrobromic acid were removed and the syrupy 2 : 3 : 6-trimethyl *d*-galactonolactone was isolated after removal of solvent at 40°. On standing, the lactone crystallised; it was purified by sublimation in a vacuum; m. p. 92°. Yield, 0·8 g. This product, further purified by recrystallisation from ether–light petroleum, had m. p. and mixed m. p. with an authentic sample, 98°. $[\alpha]_D^{20°}$ − 41° in water, initial value (Found: OMe, 41·0; equiv., 220. Calc. for $C_9H_{16}O_6$: OMe, 42·4%; equiv., 220). The lactone was converted quantitatively by solution in liquid ammonia into the amide, m. p. and mixed m. p. with an authentic specimen, 133°.

Fractions 3 and 4 were combined (0·7 g.) and hydrolysed with N-hydrochloric acid for 6 hours. The isolated sugars (0·55 g.) gave on oxidation crystalline 2 : 3 : 6-trimethyl *d*-galactonolactone, m. p. and mixed m. p. 98°, in 50% yield.

Hydrolysis of the Fraction Insoluble in Methyl Iodide.—A portion of the methylated polysaccharide (4·0 g.) was hydrolysed as described above and the methyl glycosides (4·5 g.) distilled giving: Fraction 5 (0·28 g.), b. p. 115—135°/0·001 mm., $n_D^{21°}$ 1·4532 (Found: OMe, 50·2%). Fraction 6 (1·59 g.), b. p. 135—145°/0·001 mm., $n_D^{21°}$ 1·4535 (Found: OMe, 51·4%). Fraction 7 (1·44 g.), b. p. 145—175°/0·001 mm., $n_D^{21°}$ 1·4548 (Found: OMe, 51·1%). Fraction 8 (0·47 g.), b. p. 175—190°/0·001 mm., $n_D^{21°}$ 1·4588 (Found: OMe, 48·8%). Fraction 9 (0·33 g.), b. p. > 190°/0·001 mm., $n_D^{21°}$ 1·4672 (Found: OMe, 43·5%). Still residue, 0·3 g.(not further examined).

Fractions 5, 6, 7, and 8 had substantially the same constants; they were combined and hydrolysed with N-hydrochloric acid for 4 hours ($[\alpha]_D^{20°}$ + 88° constant value). The solution was neutralised with

barium carbonate and the sugar isolated (3·5 g.); $n_D^{20°}$ 1·4770; $[\alpha]_D^{20°}$ + 36° (in methyl alcohol) (Found : OMe, 40·5. Calc. for $C_9H_{18}O_6$: OMe, 41·8%).

A sample of the syrup showed a change of rotation in cold 2% methyl alcoholic hydrogen chloride, similar to that shown by 2 : 3 : 6-trimethyl *d*-galactose. $[\alpha]_D^{20°}$ + 36° (initial value); + 5° (24 hours); 0° (36 hours); − 11° (56 hours); − 26° (70 hours, constant value). On oxidation with bromine (1 c.c.) in water (3 c.c.) the syrup (1·04 g.) gave 2 : 3 : 6-trimethyl *d*-galactonolactone, m. p. 97°, isolated in 85% yield. $[\alpha]_D^{20°}$ − 41° (initial value, in water) (Found : OMe, 41·2; equiv., 220. Calc. for $C_9H_{16}O_6$: OMe, 42·4%; equiv., 222).

A portion of the syrup (0·58 g.) was boiled with aniline (0·3 c.c.) and alcohol (3 c.c.) for 3 hours. On concentration a syrup was formed which crystallised only after 3 months. The crystals were tiled and purified by recrystallisation from absolute alcohol. Yield, 30 mg.; m. p. 189°, not depressed on admixture with an authentic specimen of 2 : 3 : 4 : 6-tetramethyl *d*-galactose anilide. Some 2 : 3 : 4 : 6-tetramethyl *d*-galactose (end group) is therefore present in the sugar syrup. No arabinose derivative could be detected in the products of hydrolysis.

Examination of Polysaccharide Fraction V.—Fraction V, the last fraction from the fractionation of the methylated polysaccharides with light petroleum (b. p. 40—60°), was purified by extraction with boiling light petroleum. The residual white solid (1·8 g.) [Found : dimethyl pentosan (by furfuraldehyde estimation), 19·4%; OMe, 40%] was subjected to methanolysis with boiling methyl alcoholic hydrogen chloride (3%) for 7 hours. The resulting methylglycosides (1·8 g.) were fractionally distilled giving : Fraction 10 (0·21 g.), b. p. 100°/0·01 mm., $n_D^{20°}$ 1·4355 (Found : OMe, 61%). Fraction 11 (0·24 g.), b. p. 100—120°/0·001 mm., $n_D^{20°}$ 1·4440. Fraction 12 (0·57 g.), b. p. 130—150°/0·01 mm., $n_D^{20°}$ 1·4568.

Fraction 10 (0·21 g.) was hydrolysed with N-hydrochloric acid (10 c.c.). $[\alpha]_D^{21°}$ − 47° (initial) fell to − 15° (constant value) in 2 hours. The syrupy sugar (0·19 g.) [Found : OMe, 43. Calc. for trimethyl *l*-arabinose ($C_8H_{16}O_5$) : OMe, 45·4%], after isolation, was oxidised with bromine (0·3 c.c.) in water (5 c.c.) for 2½ hours at 55°. Bromine was removed by aeration, the solution neutralised with silver carbonate, and the lactone isolated as a sticky solid which was purified on the tile and then by recrystallisation from ether–light petroleum; m. p. 29°, not depressed on admixture with an authentic specimen of 2 : 3 : 5-trimethyl *l*-arabonolactone. The lactone on treatment with methyl alcoholic ammonia gave 2 : 3 : 5-trimethyl *l*-arabonamide in quantitative yield, m. p. 134°, m. p. 135° on admixture with an authentic specimen of 2 : 3 : 5-trimethyl *l*- arabonamide.

The estimated yield of 2 : 3 : 5-trimethyl *l*-arabinose was about 8% of Fraction V, approximately one-third of the total pentosan content of the crude methylated polysaccharide. Fraction 11 was not further investigated. Fraction 12 (0·5 g.) on hydrolysis and oxidation (for details see under Fractions 1 and 2) gave 2 : 3 : 6-trimethyl *d*-galactonolactone, m. p. 98°, in 80% yield.

Identification of the Acidic Portion of the Polysaccharide as Pectic Acid by Preparation of the Degraded Poly-ester.—The polysaccharide (75 g.) was treated with boiling N-sulphuric acid at 90° for 6 hours. This process destroyed the araban and most of the galactan leaving a partly degraded pectic acid which separated as a flocculent precipitate. The insoluble portion (5 g.; equiv., 700) was filtered off and washed free from sulphuric acid, first with water and then with methanol. The solid was then boiled with 2% methyl alcoholic hydrogen chloride for 7 hours, and the insoluble residue was filtered off and washed free from hydrochloric acid with methanol. The solid was purified by dissolving in water and precipitating with ethanol. Yield 3 g. $[\alpha]_D^{20°}$ + 170° (in water) (Found : OMe, 17·9; equiv., 210. Calc. for methyl pectate : OMe, 16·3%; equiv., 190). On oxidation a sample gave mucic acid in 46% yield. Pectic acid was therefore a component of the mixture of polysaccharides (*A*).

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231. *The Reactions of* N-*Benzenesulphonylbenzisothiazolone with Aromatic Amines.*

By (the late) ERNEST W. MCCLELLAND and RAYMOND H. PETERS.

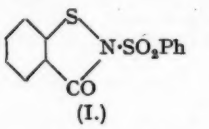
N-Benzenesulphonylbenz*iso*thiazolone (I) reacts readily with aromatic amines, the hetero-ring being opened and the sulphur atom becoming attached to the *p*-position of the amine to give substances of type (II). Hydrolysis of (II) yields the 4-amino-2′-carboxydiphenyl sulphide, which by the action of sulphuric acid undergoes ring closure to give a 2-aminothioxanthone (V). When the *p*-position of the aromatic amine is occupied by a substituent R (Me, OMe, or Cl) the sulphur atom becomes attached in the ortho-position relative to the amino-group of the amine and the product isolated is the lactam of the 2-amino-5-R-2′-carboxydiphenyl sulphide (XI), benzenesulphonamide having been eliminated. The lactam yields the free amino-acid on hydrolysis. Sulphuric acid converts these acids into 4-aminothioxanthones (XIII). 2-Amino-2′-carboxydiphenyl sulphide yields a similar lactam when boiled in xylene with phosphoric oxide.

THE reaction of *N*-benzenesulphonylbenz*iso*thiazolone (I) with aniline had been observed by McClelland and Hart (*J.*, 1939, 760), and preliminary experiments had also been made with dimethylaniline (Barton and McClelland, unpublished observations). In the present

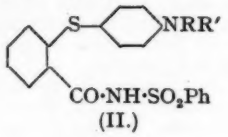
investigation the reactions with a number of aromatic amines have been studied and the nature of the products established.

The benz*iso*thiazolone condenses with one molecular proportion of the amine and several possible formulæ were considered for the products, such as (II), (III), and (IV).

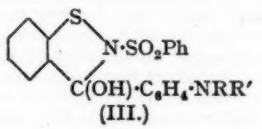
The compound from dimethylaniline is converted by heating with sulphuric acid into a dimethylaminothioxanthone. The formation of an aminothioxanthone is compatible with either formula (II) or (III) which would, however, give rise, respectively, to the 2- and 3-dimethylaminothioxanthones (V) and (VI).



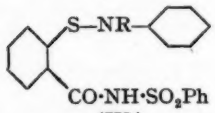
(I.)



(II.)



(III.)



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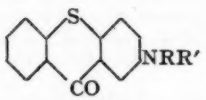
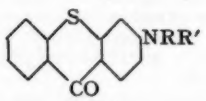


(V.)



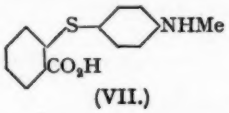
(VI.)

2-*Dimethylaminothioxanthone* (V, R = R′ = Me) was synthesised by a variation of Mayer's method (*Ber.*, 1909, **42**, 3046) as follows. The action of *p*-dimethylaminothiophenol on diazotised anthranilic acid yielded 4-dimethylamino-2′-carboxydiphenyl sulphide, which was converted by sulphuric acid into the required 2-dimethylaminothioxanthone found to be identical with the substance under discussion above. The condensation product from dimethylaniline is therefore of type (II) and not (III).

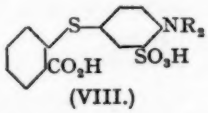
Similar results were obtained on using methylethylaniline and benzylmethylaniline, the aminothioxanthone being independently synthesised in the former case.

The product of reaction with monomethylaniline was hydrolysed to an acid which must be (VII) since it gives an acetyl derivative. This excludes formula (IV) for this condensation product, and points to formula (II, R = H, R′ = Me). The substance also yields a thioxanthone, which by analogy must be 2-*methylaminothioxanthone*.

The substance formed by condensation of the benz*iso*thiazolone with aniline is now found to contain a free primary amino-group and is converted by sulphuric acid into 2-aminothioxanthone. This compound therefore has the structure (II, R = R′ = H). In the production of the thioxanthones, sulphonic acids of the type (VIII) are also obtained. With *o*-toluidine an analogous condensation occurred.



(VII.)



(VIII.)

Benzylamine and phenylhydrazine do not condense with the benz*iso*thiazolone in boiling alcohol, but cause opening of the ring and yield di-*N*-benzenesulphonyl-2 : 2′-dithiobenzamide.

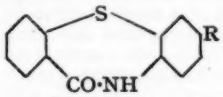
On the other hand when the *N*-benzenesulphonylbenz*iso*thiazolone was condensed with para-substituted amines a different reaction occurred, benzenesulphonamide being eliminated. The thiazolone reacted in this manner with *p*-toluidine, *p*-anisidine, and *p*-chloroaniline, but did not react with weaker bases such as the nitroanilines or anthranilic acid. The products were of high melting point and inert to bromine; they gave no colour with ferric chloride, were neither acidic nor basic, and gave no reaction for a keto-group. Their composition corresponded with that of the respective aryl*iso*thiazolone (I, C_6H_4X in place of SO_2Ph) or an isomer of it.

N-*p*-Tolylbenz*iso*thiazolone, however, prepared by the action of 2-chlorothiobenzoyl chloride on *p*-toluidine, was found to be an entirely different substance from the condensation product from *p*-toluidine.

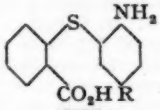
In view of the mode of reaction of benzylamine and phenylhydrazine with the benz*iso*thiazolone, mentioned above, the possibility was considered that a disulphide $\left(C_6H_4\langle^{S}_{CO\cdot NHR}\right)_2$ had been formed, the difference in composition being negligible. But, again, the disulphide prepared by the action of *p*-toluidine on 2 : 2′-dithiobenzoyl chloride was entirely different from the product under discussion: moreover the molecular weight of the corresponding substance

resulting from the reaction of *p*-anisidine with the benz*iso*thiazolone was not double as would be required for the disulphide.

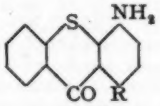
The condensation product yielded a *dioxide* soluble in aqueous sodium hydroxide and reprecipitated unchanged on acidification. Both the condensation product and its dioxide yielded monoacetyl derivatives. These were finally identified as lactams of the structure (XI) since hydrolysis with 55—65% sulphuric acid yielded in each case an aminocarboxylic acid. A thioxanthone is formed at the same time, which is evidently the result of further action of the sulphuric acid on the amino-acid. The acids must have the structure (XII) which should give 4-aminothioxanthones (XIII). This was confirmed by preparing 4-amino-1-methylthioxanthone from *o*-mercaptobenzoic acid and *p*-toluenesulphon-*p*-toluidide in sulphuric acid (cf. Ullmann and Glenck, *Ber.*, 1916, **49**, 2499); the product was identical with the thioxanthone from the amino-acid derived from the condensation product of *p*-toluidine and the benzenesulphonylbenz*iso*thiazolone.



(XI.)



(XII.)

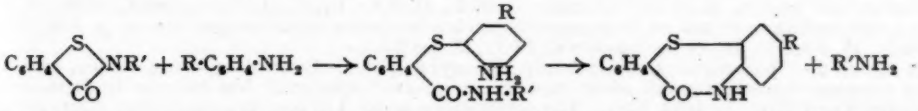


(XIII.)

The condensation products in question are thus lactams of the amino-acids of type (XII). These acids when heated with alcoholic hydrochloric acid were partly converted into the lactam. Acetic anhydride or phosphoric oxide also regenerated the lactam (XI) together with some of the thioxanthone in the latter case.

The seven-membered ring here present is not unusual in view of the presence of two *o*-phenylene groups, but it was thought desirable to provide the following confirmatory evidence. The parent sulphide, 2-amino-2′-carboxydiphenyl sulphide (Mayer, *loc. cit.*) with phosphoric oxide yielded a corresponding cyclic lactam together with some 4-aminothioxanthone. This was entirely similar in behaviour to the condensation products from *N*-benzenesulphonylbenz-*iso*thiazolone with para-substituted amines. Oxidation also gave a sulphone of similar properties, and this too was prepared independently from the sulphone of 2-nitro-2′-carboxydiphenyl sulphide.

The reaction of the benz*iso*thiazolone with para-substituted amines therefore proceeds thus :



and it follows that the products should be independent of the particular radical R′ present. This was confirmed by causing the *N*-*p*-toluenesulphonylbenz*iso*thiazolone to react with *p*-anisidine; the product was identical with that from *N*-benzenesulphonylbenz*iso*thiazolone.

Attempts to bring about reaction between dimethylaniline and *N*-methyl-, *N*-phenyl-, *N*-*p*-tolyl-, *N*-*p*-nitrophenyl-, or *N*-benzoyl-benz*iso*thiazolone gave negative results, and it appears that this type of reaction of the arylsulphonylbenz*iso*thiazolones depends on the joint action of the SO_2 and CO groups attached to the same nitrogen atom, the simultaneous presence of which facilitates the rupture of the heterocyclic ring.

Experimental.

Reaction of N-*Benzenesulphonylbenz*iso*thiazolone with Tertiary Aromatic Amines.*—The benz*iso*thiazolone (5 g.) was boiled in alcohol (20 ml.) with the amine (5 g.) until all the former had dissolved (3 hrs.). The product crystallised on cooling. *4-Dimethylamino-2′-N-benzenesulphonylcarbamyldiphenyl sulphide* was thus obtained from dimethylaniline, as yellow needles from alcohol, m. p. 172° (Found : C, 61·6; H, 4·7. $C_{21}H_{20}O_3N_2S_2$ requires C, 61·1; H, 4·9%). In his examination of this substance Dr. A. W. H. Barton isolated a *sodium* salt sparingly soluble in water crystallising from alcohol in white needles, m. p. 308° (Found : Na, 5·4. $C_{21}H_{19}O_3N_2S_2Na$ requires Na, 5·3%), and by methylation with methyl sulphate a *methyl* derivative, white needles from methyl alcohol, m. p. 144° (Found : C, 62·0; H, 5·2. $C_{22}H_{22}O_3N_2S_2$ requires C, 62·0; H, 5·2%), which on hydrolysis with acid yielded benzenesulphonmethylamide, m. p. 31°. The original condensation product was hydrolysed by boiling for 2 hours with concentrated hydrochloric acid, and the mixture poured into water, made alkaline with sodium hydroxide, and finally acidified with acetic acid. The greenish precipitate was purified by crystallisation of the sodium salt, reconversion into the acid and crystallisation from alcohol; it formed small greenish needles, m. p. 250—260° (decomp.). *4-Dimethylamino-2′-carboxydiphenyl sulphide* so obtained was identical with that prepared synthetically as follows. *pp′*-Bisdimethylaminodiphenyl disulphide (10 g.) prepared by the method of Merz and Weith (*Ber.*, 1869, **22**, 1571) was reduced by

warming with tin (3 g.) and concentrated hydrochloric acid (30 c.c.), the solution made alkaline (100 c.c. of 35% aqueous sodium hydroxide) and heated while a stream of nitrogen was passed through the flask, and a diazotised solution of anthranilic acid (8·8 g.) slowly added. After 5 minutes' boiling and cooling the grey-green sodium salt which separated was collected and dissolved in water, and the free acid precipitated by adding acetic acid. It was apparently identical with the hydrolysis product described above (Found on a sample from alcohol, dried in a vacuum: C, 64·9; H, 5·7. After drying at 110°: C, 66·4; H, 5·9. $C_{15}H_{15}O_2NS,C_2H_6O$ requires C, 64·0; H, 6·6%. $C_{15}H_{15}O_2NS$ requires C, 66·0; H, 5·5%). The presence of alcohol in the former specimen was confirmed by an iodoform test.

In view of the indefiniteness of the melting point of this substance the *ethyl* ester was prepared from both the hydrolysis product and the synthetic acid. In each case it formed white needles from alcohol, m. p. 143° (not depressed by mixture of the two). For analysis the substance was purified by molecular distillation (Found: C, 67·5, 67·5; H, 6·8, 6·4. $C_{17}H_{19}O_2NS$ requires C, 67·7; H, 6·4%). Other amines yielded the corresponding 4-aminodiphenyl sulphides. *4-Methylethylamino-2′-N-benzenesulphonylcarbamyldiphenyl sulphide* formed pale yellow plates from alcohol, m. p. 141° (Found: C, 61·1, 60·6; H, 5·6, 6·0. $C_{22}H_{22}O_3N_2S_2$ requires C, 61·7; H, 5·2. $C_{22}H_{22}O_3N_2S_2,C_2H_6O$ requires C, 61·0; H, 6·0%). On hydrolysis with concentrated hydrochloric acid it yielded *4-methylethylamino-2′-carboxydiphenyl sulphide* as a greenish microcrystalline powder, m. p. *ca.* 230° (decomp.) (Found: C, 66·8; H, 5·9. $C_{16}H_{17}O_2NS$ requires C, 66·8; H, 6·0%). This acid was also synthesised. 4 : 4′-Bismethylethylaminodiphenyl disulphide prepared by Merz and Weith's method (*loc. cit.*) formed an amorphous mass which did not crystallise and was used in the crude form. It was reduced to the thiol as described above, and with diazotised anthranilic acid gave the 4-methylethylamino-2′-carboxydiphenyl sulphide as a pale green microcrystalline powder, m. p. *ca.* 230° (decomp.) (Found: C, 66·8; H, 5·9%). *4-Benzylmethylamino-2′-N-benzenesulphonylcarbamyldiphenyl sulphide* crystallised in pale green needles from alcohol, m. p. 123°. The crystals contain alcohol of crystallisation as shown by direct test (Found: C, 65·1; H, 5·2. $C_{27}H_{24}O_3N_2S_2$ requires C, 66·4; H, 4·9. $C_{27}H_{24}O_3N_2S_2,C_2H_6O$ requires C, 65·1; H, 5·6%). Hydrolysis with 60% sulphuric acid yielded *4-benzylmethylamino-2′-carboxydiphenyl sulphide*, which crystallised from alcohol as a pale green microcrystalline powder, m. p. 194° (Found: C, 71·7; H, 5·0. $C_{21}H_{19}O_2NS$ requires C, 72·1; H, 5·5%).

4-Methylamino-2′-N-benzenesulphonylcarbamyldiphenyl sulphide separated from alcohol in white plates which turned green on exposure to air, m. p. 142° (Found: C, 60·5; H, 4·4. $C_{20}H_{18}O_3N_2S_2$ requires C, 60·3; H, 4·5%). The *nitroso*-derivative crystallised from alcohol in golden needles, m. p. 170° (Found: C, 56·0; H, 4·1. $C_{20}H_{17}O_4N_3S_2$ requires C, 56·1; H, 4·0%). Hydrolysis with 60% sulphuric acid yielded *4-methylamino-2′-carboxydiphenyl sulphide*, small needles from butyl alcohol, m. p. 215° (Found: C, 64·9; H, 5·5. $C_{14}H_{13}O_2NS$ requires C, 64·8; H, 5·1%). The *acetyl* derivative formed white plates, m. p. 209° (Found: C, 63·4; H, 5·3. $C_{16}H_{15}O_3NS$ requires C, 63·8; H, 5·0%).

4-Ethylamino-2′-N-benzenesulphonylcarbamyldiphenyl sulphide separated from aqueous alcohol in cream coloured crystals, m. p. 150° (Found: C, 61·0; H, 5·1. $C_{21}H_{20}O_3N_2S_2$ requires C, 61·1; H, 4·9%). The *nitroso*-derivative crystallised from alcohol in small red prisms which turned yellow on heating, m. p. 138° (Found: C, 56·7; H, 4·3. $C_{21}H_{19}O_4N_3S_2$ requires C, 57·1; H, 4·4%). Hydrolysis with 60% sulphuric acid yielded *4-ethylamino-2′-carboxydiphenyl sulphide*, which crystallised from butyl alcohol in buff needles, m. p. 224° (Found: C, 65·6; H, 5·4. $C_{15}H_{15}O_2NS$ requires C, 65·0; H, 5·5%). The *acetyl* derivative separated from aqueous alcohol in almost colourless needles, m. p. 184° (Found: C, 64·7; H, 5·4. $C_{17}H_{17}O_3NS$ requires C, 64·7; H, 5·4%).

4-Amino-2′-*N*-benzenesulphonylcarbamyldiphenyl sulphide, obtained by using aniline, crystallised from aqueous alcohol in small white needles, m. p. 167° (analysed, but incorrectly formulated by McClelland and Hart, *J.*, 1939, 760). The *perchlorate* separated in minute needles from dilute perchloric acid, m. p. 221° (decomp.) (Found: C, 45·5, 45·7; H, 4·1, 4·0. Found after drying at 100°: C, 45·0; H, 3·4. $C_{19}H_{17}O_7N_3ClS_2,H_2O$ requires C, 45·4; H, 3·8%. $C_{19}H_{17}O_7N_3ClS_2$ requires C, 45·4; H, 3·8%). Diazotisation and coupling with alkaline β-naphthol gave the corresponding *azo-β-naphthol*, which crystallised in red prisms from ethyl acetate or acetone, m. p. 148° (Found: C, 64·0, 64·0; H, 4·1, 4·1. $C_{29}H_{21}O_4N_3S_2$ requires C, 64·5; H, 3·9%). The filtered diazo-solution after addition of urea and boiling yielded 4-hydroxy-2′-*N*-benzenesulphonylcarbamyldiphenyl sulphide, which separated from hot water in small white needles, m. p. 143°. Hydrolysis with 60% sulphuric acid yielded 4-amino-2′-carboxydiphenyl sulphide, which after crystallisation from aqueous alcohol had m. p. 193° not depressed by admixture of an authentic specimen prepared from the nitro-acid obtained from *p*-nitrothiophenol and anthranilic acid (cf. Mayer, *loc. cit.*).

Reaction with *o*-toluidine produced *4-amino-2′-N-benzenesulphonylcarbamyl-3-methyldiphenyl sulphide*, which after purification through the perchlorate crystallised from alcohol in white needles, m. p. 118° (Found: C, 59·7; H, 5·3. $C_{20}H_{18}O_3N_2S_2,C_2H_6O$ requires C, 59·4; H, 5·4%). The *perchlorate* formed cream coloured needles from dilute perchloric acid, m. p. 225° (decomp.) (Found: C, 48·6; H, 4·0. $C_{20}H_{19}O_7N_2ClS_2$ requires C, 48·2; H, 3·8%). The corresponding *azo-β-naphthol* crystallised from ethyl acetate in dark red prisms, m. p. 136° (Found: C, 65·0; H, 4·6. $C_{30}H_{23}O_4N_3S_2$ requires C, 65·1; H, 4·2%).

Action of Sulphuric Acid on the Foregoing Aminodiphenyl Sulphides.—The 4-substituted 2′-*N*-benzenesulphonylcarbamyldiphenyl sulphides were warmed at 50° for 1 hour with concentrated sulphuric acid (20 c.c. for 5 g.). The resulting solution on being poured into water gave a white precipitate of a sulphonic acid, and addition of alkali to the filtered solution yielded an aminoxanthone, a further yield of which was obtained by redissolving the sulphonic acid in alkali.

2-Dimethylaminothioxanthone crystallised from alcohol in orange needles, m. p. 122° (Found: C, 70·4; H, 5·3; N, 5·7. $C_{15}H_{13}ONS$ requires C, 70·5; H, 5·1; N, 5·5%). The substance gave a green fluorescence in sulphuric acid solution. It was found by m. p. and mixed m. p. to be identical with the xanthone produced by the action of concentrated sulphuric acid on synthetic 4-dimethylamino-2′-carboxydiphenyl sulphide (see above).

The sulphonic acid was purified by precipitation from alkaline solution, redissolved and boiled in

alkali with charcoal, reprecipitated, and finally boiled with water. It was a white microcrystalline powder, m. p. 318°, presumably *4-dimethylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid*, but the position of the sulphonic acid group was not proved (Found: C, 50·9; H, 4·1; N, 3·6. $C_{15}H_{15}O_5NS_2$ requires C, 51·0; H, 4·2; N, 3·9%). When this substance was heated in concentrated sulphuric acid (10 parts) for ½ hour at 150° a brown solution with green fluorescence was formed. The solution was diluted and made alkaline, the dark red mass deposited was dissolved in water, and the solution was acidified. The acid precipitated was crystallised from hot water and formed a light brown microcrystalline powder not melting at 310°. The substance was hygroscopic and analyses were unsatisfactory, but it was presumably *2-dimethylaminothioxanthone-3-sulphonic acid* (Found: C, 49·8; H, 4·3. Found after drying at 100° in a vacuum: C, 51·9; H, 4·5. $C_{15}H_{13}O_4NS_2,H_2O$ requires C, 51·0; H, 4·3%. $C_{15}H_{13}O_4NS_2$ requires C, 53·7; H, 3·9%). The sodium salt had m. p. 310°; the *potassium* salt was a dihydrate (Found: H_2O, 6·8. $C_{15}H_{12}O_4NS_2K,2H_2O$ requires H_2O, 6·8%) and had m. p. 95° or, after heating at 100° in a vacuum, m. p. 230°.

2-Methylethylaminothioxanthone was similarly obtained and crystallised from alcohol in pale orange needles, m. p. 120° (Found: C, 70·9; H, 5·6. $C_{16}H_{15}ONS$ requires C, 71·3; H, 5·6%). This compound was identified by m. p. and mixed m. p. with that obtained by the action of sulphuric acid on synthetic 4-methylethylamino-2'-carboxydiphenyl sulphide (see above).

The accompanying sulphonic acid formed white needles from hot water, m. p. 314° (decomp.), and was *4-methylethylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid* (Found: C, 52·6; H, 4·6. $C_{16}H_{17}O_5NS_2$ requires C, 52·3; H, 4·6%). The sodium salt had m. p. 272°, the potassium salt m. p. 215°. *2-Benzylmethylaminothioxanthone* crystallised from alcohol in yellow needles, m. p. 149·5° (Found: C, 76·2; H, 5·4. $C_{21}H_{17}ONS$ requires C, 76·1; H, 5·2%). *4-Benzylmethylamino-2'-carboxydiphenyl sulphide 3-sulphonic acid* was a microcrystalline powder sparingly soluble in hot water, m. p. 286° (decomp.) (Found: C, 58·9; H, 4·6. $C_{21}H_{19}O_5NS_2$ requires C, 58·7; H, 4·5%).

2-Methylaminothioxanthone crystallised from aqueous alcohol in small yellow needles, m. p. 158°, or minute red crystals becoming yellow at *ca.* 144° (Found: C, 70·0; H, 4·5. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·6%). The accompanying *4-methylamino-2'-carboxydiphenyl sulphide-3-sulphonic acid* formed white needles from hot water, m. p. 321° (decomp.) (Found: C, 46·3; H, 4·2. $C_{14}H_{13}O_5NS$ requires C, 49·6; H, 3·8. $C_{14}H_{13}O_5NS,H_2O$ requires C, 47·0; H, 4·2%).

2-Ethylaminothioxanthone was obtained as orange plates or needles from alcohol, m. p. 134° (Found: C, 70·3; H, 5·1. $C_{15}H_{13}ONS$ requires C, 70·5; H, 5·1%). No sulphonic acid was isolated in this case.

2-Aminothioxanthone formed yellow needles from alcohol or plates from nitrobenzene, m. p. 227° (Found: C, 69·3, 70·0; H, 3·7, 4·3. Calc.: C, 68·7; H, 4·0%. Cf. Mayer, *loc. cit.*, who also reports poor analyses). It was shown to be identical with the aminothioxanthone synthesised (in poor yield) by the method of Smiles (*J.*, 1911, 2046) or by that of Mayer (*loc. cit.*).

This substance, boiled with acetic anhydride in toluene solution for 4 hours, yielded a *diacetyl* derivative which crystallised from toluene in yellow crystals, m. p. 245° (Found: C, 65·3; H, 3·9. $C_{17}H_{13}O_3NS$ requires C, 65·6; H, 4·2%). On hydrolysis it furnished the parent aminoxanthone.

In its production from the condensation product from aniline it was accompanied by *4-amino-2'-carboxydiphenyl sulphide-3-sulphonic acid*, which separated in small white crystals from water, m. p. > 320° (Found: C, 48·0; H, 3·5. $C_{13}H_{11}O_5NS_2$ requires C, 48·0; H, 3·4%).

Reaction of N-Benzenesulphonylbenzisothiazolone with p-*Substituted Aromatic Amines. Formation of the Lactams of the 2-Amino-2'-carboxydiphenyl Sulphides.*—The thiazolone was heated for 5 hours in boiling alcohol with an equal weight of *p*-toluidine, the solution evaporated to dryness, and the product recrystallised from alcohol or glacial acetic acid. The *lactam* of *2-amino-2'-carboxy-5-methyldiphenyl sulphide* was thus isolated as glistening plates, m. p. 274° (Found: C, 69·2; H, 4·5. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·6%). Benzenesulphonamide was found in the mother liquors. The lactam was oxidised by hydrogen peroxide in acetic acid to its *sulphone*, a white microcrystalline powder, m. p. > 320° (Found: C, 61·5; H, 4·1. $C_{14}H_{11}O_3NS$ requires C, 61·4; H, 4·1%). The lactam was hydrolysed by boiling it for 4 hours with 65% sulphuric acid. On dilution a precipitate was formed containing the sulphate of the amino-acid, and a thioxanthone, separated by dissolving the former out in alkali. The residue was 4-amino-1-methylthioxanthone, yellow needles from alcohol, m. p. 183° not depressed by admixture of a specimen prepared by the method of Ullmann and Glenck (*Ber.*, 1916, **49**, 2499). The alkaline solution, on acidification with acetic acid, gave a *2-amino-2'-carboxy-5-methyldiphenyl sulphide*, which crystallised from butyl alcohol in pale buff needles, m. p. 170° (Found: C, 65·2; H, 5·1. $C_{14}H_{13}O_2NS$ requires C, 64·9; H, 5·1%). The acid was re-converted by boiling in acetic anhydride for ½ hour or by standing overnight in sulphuric acid solution into the lactam, m. p. 271°. The lactam was also formed when the acid was heated for 3 hours in boiling ethyl alcohol containing 2—5% of hydrogen chloride, and the ethyl ester of the acid, m. p. 100°, was also produced. When the acid was heated in boiling xylene for ½ hour with phosphoric oxide it yielded the lactam together with 4-amino-1-methylthioxanthone.

The thiazolone with *p*-anisidine furnished the *lactam* of *2-amino-2'-carboxy-5-methoxydiphenyl sulphide*, which crystallised from alcohol in white needles, m. p. 235° (Found: C, 64·9; H, 4·1; *M*, ebullioscopic in alcohol, 250. $C_{14}H_{11}O_2NS$ requires C, 65·3; H, 4·3%; *M*, 241). The *acetyl* derivative formed white needles from alcohol, m. p. 165° (Found: C, 63·7; H, 4·6. $C_{16}H_{13}O_3NS$ requires C, 64·2; H, 4·4%). The *sulphone* separated as a microcrystalline powder from acetic acid, m. p. 246° (Found: C, 58·3; H, 4·2. $C_{14}H_{11}O_4NS$ requires C, 58·1; H, 3·8%), which also yielded an *acetyl* derivative, m. p. 194° (Found: C, 58·5; H, 4·0. $C_{16}H_{13}O_5NS$ requires C, 58·0; H, 3·9%).

The same lactam was obtained when *N-p*-toluenesulphonylbenz*iso*thiazolone was used in place of the benzenesulphonyl derivative. Hydrolysed by acid it furnished the *2-amino-2'-carboxy-5-methoxydiphenyl sulphide*, which crystallised from dilute acetic acid or butyl alcohol in buff needles, m. p. 168° (Found: C, 61·5; H, 4·9. $C_{14}H_{13}O_3NS$ requires C, 61·1; H, 4·8%), and formed a *perchlorate*, which separated from dilute perchloric acid as a white microcrystalline powder, m. p. 210° (decomp.) (Found: C, 43·3; H, 4·5. $C_{14}H_{14}O_3NClS,H_2O$ requires C, 42·9; H, 4·1%). As a by-product in the hydrolysis a

substance was isolated which crystallised from glacial acetic acid in red needles, m. p. 238°, and appeared to be 4-*amino*-1-*hydroxythioxanthone* (Found: C, 63·0; H, 3·8. $C_{13}H_9O_2NS$ requires C, 63·5; H, 3·8%). The acid kept overnight in sulphuric acid solution yielded 4-*amino*-1-*methoxythioxanthone*, yellow plates from alcohol, m. p. 168° (Found: C, 64·9; H, 4·4. $C_{14}H_{11}O_2NS$ requires C, 65·3; H, 4·3%).

The action of *p*-chloroaniline on *N*-benzenesulphonylbenz*iso*thiazolone (12 hours' boiling) yielded the *lactam* of 5-*chloro*-2-*amino*-2′-*carboxydiphenyl sulphide*, which crystallised from glacial acetic acid in colourless plates, m. p. 321° (Found: C, 59·0; H, 3·4. $C_{13}H_8ONClS$ requires C, 59·6; H, 3·1%). Hydrolysis with 65% sulphuric acid gave the *acid*, which separated from dilute acetic acid as a microcrystalline powder, m. p. 183° (Found: C, 55·1; H, 3·8. $C_{13}H_{10}O_2NSCl$ requires C, 55·8; H, 3·6%).

Lactam of 2-Amino-2′-carboxydiphenyl Sulphide.—2-Amino-2′-carboxydiphenyl sulphide of m. p. 157° prepared Mayer's method (*loc. cit.*), when heated with phosphoric oxide in boiling xylene for ½ hour, gave the *lactam*, which crystallised from acetic acid in colourless plates, m. p. 256° (Found: C, 68·4; H, 4·2. $C_{13}H_9ONS$ requires C, 68·7; H, 4·4%). Oxidation with hydrogen peroxide in acetic acid yielded the *lactam sulphone*, which separated from dilute acetic acid in colourless needles, m. p. 290° (Found: C, 60·4; H, 3·8. $C_{13}H_9O_3NS$ requires C, 60·1; H, 3·5%). These lactams are soluble in warm aqueous sodium hydroxide. The same lactam sulphone was also obtained from 2-nitro-2′-carboxydiphenyl sulphone (Mayer, *loc. cit.*) by reduction to the amino-acid sulphone and heating the latter with phosphoric oxide in xylene.

p-*Toluidide and* p-*Nitroanilide of Dithiobenzoic Acid.*—2 : 2′-Dithiobenzoyl chloride reacted with *p*-toluidine or *p*-nitroaniline in carbon tetrachloride or toluene solution, yielding the p-*toluidide*, m. p. 233° (Found: C, 69·2; H, 5·1. $C_{28}H_{24}O_2N_2S_2$ requires C, 69·4; H, 5·0%), and the p-*nitroanilide*, which crystallised from aqueous pyridine in light brown needles, m. p. 263° (Found: C, 57·0; H, 3·5. $C_{26}H_{18}O_6N_4S_2$ requires C, 57·1; H, 3·3%).

N-*Arylbenz*iso*thiazolones.*—Chlorine was passed into 2 : 2′-dithiobenzoyl chloride (10 g.) covered with carbon tetrachloride (60 c.c.) until it had dissolved, the excess of chlorine removed by a current of nitrogen, and the resulting solution added to an ice-cooled solution of *p*-toluidine (20 g.) in carbon tetrachloride (200 c.c.). The dark solution was filtered and evaporated, and the product crystallised from methyl alcohol (charcoal). N-p-*Tolylbenz*iso*thiazolone* was thus obtained as colourless needles, m. p. 135° (Found: C, 69·3; H, 4·3. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·5%). A similar condensation with *p*-nitroaniline using pyridine as solvent yielded N-p-*nitrophenylbenz*iso*thiazolone*, a microcrystalline powder from acetic acid, m. p. 238° (Found: C, 57·1; H, 3·2. $C_{13}H_8O_3N_2S$ requires C, 57·3; H, 3·0%). This substance was also obtained by adding to the *p*-toluidide of dithiobenzoic acid (3 g.) covered with carbon tetrachloride (50 c.c.) a solution of bromine (2 g.) in carbon tetrachloride (10 c.c.). The dirty red precipitate of bromo-thiol was removed by filtration and boiled with acetic acid (100 c.c.). The thiazolone crystallised on cooling, m. p. 238°. Oxidation by hydrogen peroxide in hot acetic acid converted it into N-p-*nitrophenylsaccharin*, pale yellow plates from acetic acid, m. p. 229° (Found: C, 50·8; H, 2·4. $C_{13}H_8O_5N_2S$ requires C, 51·3; H, 2·6%).

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232. *A Method of Synthesis of Trinitromethane Derivatives.*

By W. S. REICH and (in part) G. G. ROSE and W. WILSON.

The present investigations have shown that aromatic halogenomethyl derivatives react with the silver salt of *aci*-trinitromethane yielding trinitromethane derivatives. They are stable, crystalline, colourless compounds, most probably of the true nitro-type. The reaction also yields varying amounts of unstable, deeply coloured derivatives, probably of the *aci*-trinitromethane type.

A number of trinitromethyl and polytrinitromethyl derivatives were prepared by this method, all of which contained the trinitromethyl group in the side chain of the benzene nucleus. The benzene nucleus itself was in many cases either nitrated or polynitrated.

Improved or new methods for the preparation of a number of intermediary products are also described.

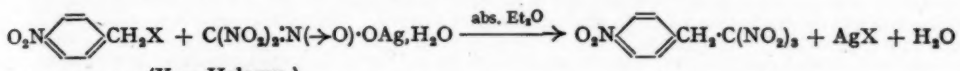
TRINITROMETHANE (nitroform) was first prepared by Schischkoff (*Annalen*, 1857, **101**, 216) by the action of water or alcohol on trinitromethyl cyanide, and later several methods for its preparation from tetranitromethane were described (Hantzsch and Rinkenberger, *Ber.*, 1899, **32**, 635; Chattaway and Harrison, *J.*, 1916, **109**, 171; Macbeth and Orr, *J.*, 1932, 534). A number of addition compounds of trinitromethane, such as its salts with pyridine, piperidine, and dibenzylamine, have also been prepared (Schmidt and Fischer, *Ber.*, 1920, **53**, 1529); they are very unstable and soon decompose on keeping.

Two aliphatic trinitromethane derivatives, *viz.*, 1 : 1 : 1-trinitroethane and hexanitroethane, have been described. Franchimont (*Rec. Trav. chim.*, 1886, **5**, 282) obtained the former by the action of concentrated nitric acid on methylmalonic acid, and it was later prepared (Hantzsch and Rinkenberger, *loc. cit.*) by reaction between silver trinitromethane and methyl iodide, but

this silver salt and iodotrinitromethane failed to give hexanitroethane. All attempts to use higher halogeno-paraffins, such as ethyl or butyl iodide, instead of methyl iodide, with a view to obtain other trinitromethane derivatives failed to yield any pure or stable compound. Will (*Ber.*, 1914, **47**, 963) obtained hexanitroethane by the action of concentrated nitric and sulphuric acids on the potassium salt of 1 : 1 : 2 : 2-tetranitroethane.

Ponzio (*Gazzetta*, 1932, **62**, 503) obtained aromatic azo-derivatives of trinitromethane [*e.g.*, *p*-Cl·C$_6$H$_4$·N:N·C(NO$_2$)$_3$] by the reaction of ammonium trinitromethane with aromatic diazonium salts. They form yellow or orange crystalline compounds, which rapidly decompose on standing or in solution.

The present investigation has shown that it is possible to prepare stable, crystalline, aromatic trinitromethane derivatives. The synthesis was carried out by reaction of the silver salt of trinitromethane with halogenomethyl derivatives of the aromatic series :



(X = Halogen.)

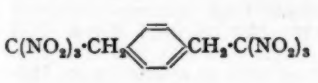
It is noteworthy that the *aci*-trinitromethane group of the silver salt is rearranged to the true nitro-type very probably contained in the stable, colourless trinitromethane derivative. The reaction also yields an unstable, deeply coloured, trinitromethane derivative, probably of the *aci*-trinitro-type, which slowly decomposes with elimination of nitrous fumes. The yield of this unstable compound depends on the working conditions and on the nature of the aromatic group. Substitution of negative groups in the benzene nucleus, especially in the *p*-position, increases the yield of the stable compound.

All the trinitromethane derivatives described in this investigation are very stable : after 3 years' standing in stoppered bottles at room temperature, they showed no change.

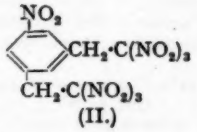
(With G. G. Rose.) The preparation of the 2 : 4 : 6-trinitrobenzyl derivative by the same method proceeds easily, and the yield of the stable compound (presumably of the true nitro-type) is greater (64%) than that of the *p*-nitrobenzyl derivative (45%). In both cases, there was also formed a small amount of an unstable deeply coloured oil, presumably a mono-*aci*-compound or a mixture derived from it by decomposition and secondary reactions.

Attempts to cause reaction between 2 : 4 : 6-trinitrobenzyl bromide and the silver salt of *aci*-trinitromethane were unsuccessful, but the iodide afforded 2 : 4 : 6-*trinitro*-2′ : 2′ : 2′-*trinitroethylbenzene*.

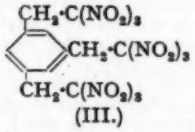
(With W. Wilson.) The same reaction was utilised for the synthesis of some polytrinitromethyl derivatives : *p*-xylylene di-iodide, ωω′-*di-iodo*-5-*nitro*-m-*xylene*, and ωω′ω″-*tri-iodomesitylene* reacted with an etheral solution of silver *aci*-trinitromethane to yield, respectively, 1 : 4-*bis*-2′ : 2′ : 2′-*trinitroethylbenzene* (I), 5-*nitro*-1 : 3-*bis*-2′ : 2′ : 2′-*trinitroethylbenzene* (II), and 1 : 3 : 5-*tris*-2′ : 2′ : 2′-*trinitroethylbenzene* (III).



(I.)



(II.)



(III.)

Experimental.

Silver Salt of Trinitromethane.—This preparation has been described by Hantzsch and Rinkenberger (*loc. cit.*), but for the preparation of larger quantities of pure material the following method is better. Silver oxide (freshly prepared, still slightly damp, 265 g.) was cautiously and gradually added to a solution of trinitromethane (180 g.) in ether (1000 c.c.); after each addition the mixture was shaken for a short while, and when the addition was complete the mixture was vigorously shaken over-night. The solution was separated by filtration, and the low-boiling material removed under reduced pressure, the ether at room temperature, and the remaining liquid at 42° (bath temp.)/12 mm. The residue was kept at 42°/12 mm. for an hour after it had crystallised and was then pressed on porous plates. A typical yield was 260 g. (*ca.* 70%).

p-*Nitrobenzyltrinitromethane.*—*p*-Nitrobenzyl bromide (85 g.) was dissolved in dry ether (1800 c.c.), the solution stirred in a water-bath at 20°, and a solution of the silver salt of trinitromethane (109 g.) in ether (600 c.c.) gradually added. After the addition was complete, the stirring was continued for about 2 hours and the mixture was left in the water-bath for 48 hours. The precipitated silver bromide was then filtered off, washed with ether, and dried in a desiccator (76 g. Calc. : 75 g.). The filtrate was concentrated in a high-speed evaporation apparatus at 25° (bath temp.)/12 mm., and the residue, consisting of a red liquid and a solid, was left on the vacuum pump at 30° (bath temp.) for about 15 minutes, and then for 2 hours in a refrigerator. The pale pink crystals were separated by filtration and

pressed on a porous plate (51 g., 45%), m. p. 129° (decomp.). The substance was dissolved in 250 c.c. of boiling absolute alcohol, the solution filtered while hot, and the filtrate kept overnight at 0°. The crystals were separated by filtration, washed with a small amount of cold absolute alcohol, and dried in a desiccator (34 g.). The substance was recrystallised from 200 c.c. of hot absolute alcohol–carbon tetrachloride (25 : 75) (yield 28 g.) and three further similar recrystallisations afforded 17 g. of pure 4-*nitro*-2′ : 2′ : 2′-*trinitroethylbenzene*; white crystals, m. p. 135° (Found : C, 33·7; H, 2·3; N, 19·5. $C_8H_6O_8N_4$ requires C, 33·6; H, 2·1; N, 19·6%).

2 : 4 : 6-*Trinitrobenzyl Bromide*.—Ganguly's method (*Ber.*, 1925, **58**, 708) was used with some modifications. Repeated crystallisation gave a substance, m. p. 71°, which was almost analytically pure (Found : Br, 26·85. Calc. for $C_7H_4O_6N_3Br$: Br, 26·14%). Ganguly gives m. p. 65° but no analysis.

2 : 4 : 6-*Trinitrobenzyl Iodide*.—Reich, Wetter, and Widmer's method (*Ber.*, 1912, **45**, 3056) was used. The brown solid was twice recrystallised from hot methyl alcohol, yielding needles, m. p. 87°; yield 47%. In general, the brominated derivative was only once crystallised before being converted into the iodo-compound, as the latter was then considerably easier to purify.

2 : 4 : 6-*Trinitro*-2′ : 2′ : 2′-*trinitroethylbenzene*.—Trinitrobenzyl iodide (105·9 g.) and ether (150 c.c.) were stirred whilst a solution of the silver salt of *aci*-trinitromethane (87 g.) in ether (280 c.c.) was added. The stirring was continued for 18 hours and the mixture filtered. The filtrate on evaporation yielded an unstable red oil which was ignored. The residue, a yellow-brown powder (140 g.), was extracted in portions with chloroform (Soxhlet), and the residues from the extraction were powdered and re-extracted with chloroform. On cooling, the chloroform extracts yielded a light brown, crystalline solid (72 g., 64%), m. p. 151·5—152·5° (decomp.). [The residue insoluble in chloroform was silver iodide (65 g. Calc. : 70 g.).] The brown crystals (72 g.) were dissolved in hot ethyl acetate (220 c.c.), the solution filtered from traces of silver iodide, chloroform (500 c.c.) added to the fairly warm filtrate, and the mixture cooled to 0°; the yellow crystals obtained (62 g.), m. p. 152·5—153·5° (decomp.), were four times recrystallised from hot ethyl nitrate–chloroform (1 : 1 by vol.), and the pure *hexanitro*-compound isolated as faintly coloured, large crystals (38 g.), m. p. 153—154° (decomp.) (Found : C, 25·8; H, 1·3; N, 22·4. $C_8H_4O_{12}N_6$ requires C, 25·5; H, 1·1; N, 22·35%).

Before each crystallisation the substance was finely powdered with an agate pestle and mortar and then dissolved with stirring in the requisite quantity of hot ethyl nitrate (about 150 c.c. to 55 g. of substance); when solution was complete an equal volume of chloroform was added, and the mixture cooled to 0° until crystallisation was complete. By this means prolonged heating, which caused extensive discolouration, was avoided.

ω-Bromo-5-nitro-m-*xylene*.—5-Nitro-*m*-xylene (2 g.) in boiling ethylene dibromide (40 c.c.) was irradiated by a 100-watt tungsten-filament lamp whilst a solution of bromine (4·3 g.) in ethylene dibromide (15 c.c.) was dropped in. After an hour the bromination was complete. Removal of the ethylene dibromide at 75°/20 mm. yielded a dark semi-solid substance, which was recrystallised from petroleum (b. p. 40—60°); yield, 500 mg. of *ω-bromo-5-nitro*-m-*xylene*, m. p. 59·5—60° (Found : C, 9·4; H, 3·4. $C_8H_8O_2NBr$ requires C, 41·7; H, 3·5%).

ωω′-Dibromo-5-nitro-m-*xylene*.—5-Nitro-*m*-xylene (m. p. 71—72·5°; 120 g.), dissolved in boiling ethylene dibromide (450 c.c.), was heated under reflux and irradiated with a 500-watt tunsten-filament lamp whilst a solution of dry bromine (100 c.c.) in ethylene dibromide (100 c.c.) was added fairly rapidly. After the bromine had almost disappeared, the ethylene dibromide was removed in a vacuum, the residue allowed to crystallise, and the crystals separated and washed with ether. Recrystallisation from petrol (b. p. 80—100°) yielded pure *ωω′-dibromo-5-nitro*-m-*xylene* (46 g.), m. p. 105—106·5° (Found : Br, 51·4. $C_8H_7O_2NBr_2$ requires Br, 51·8%).

Both the mono- and the di-bromo-compound were lachrymatory and had skin-irritant properties, and both afforded silver bromide quantitatively on treatment with warm aqueous-alcoholic silver nitrate.

ωω′-Di-iodo-5-nitro-m-*xylene*.—The crude dibromo-compound (above) (62 g.) was added to a solution of sodium iodide (85 g.) in acetone (400 c.c.); after 1 hour's heating under reflux the acetone was distilled off, and the residue washed with water. The product, crystallised from benzene–petroleum (b. p. 40—60°), yielded 53 g. of pure *ωω′-di-iodo-5-nitro*-m-*xylene*, m. p. 136—137° (Found : N, 3·6. $C_8H_7O_2NI_2$ requires N, 3·5%).

5-*Nitro*-1 : 3-*bis*-2′ : 2′ : 2′-*trinitroethylbenzene*.—(i) ωω′-Dibromo-5-nitro-*m*-xylene (m. p. 102—105°; 8 g.) was suspended in ether (100 c.c.) and 48·8 c.c. of a solution of the silver salt of trinitromethane (containing 297·4 g. per l. of ether) were added slowly. After 3 days, the silver bromide (10 g.) was filtered off, the filtrate washed with water, and then desolvated at 30°/20 mm.; the semi-solid residue was triturated with chloroform at 0°, yielding crystals (0·9 g.), m. p. 158—160°. Recrystallisation from chloroform yielded the pure *heptanitro*-compound, m. p. 170—171·5° (slight decomp.) (Found : C, 26·6; H, 1·8; N, 21·8. $C_{10}H_7O_{14}N_7$ requires C, 26·7; H, 1·6; N, 21·8%).

(ii) ωω′-Di-iodo-5-nitro-*m*-xylene (50 g.) was suspended in dry ether (500 c.c.), and 280 c.c. of an ethereal solution of the silver salt of trinitromethane (containing 248 g. per l.) were added fairly rapidly at 18—25° with vigorous stirring. After the stirring had continued for 4 hours, the silver iodide (61 g.) was filtered off, and the filtrate washed with water and dried (Na_2SO_4). The ether was removed in a vacuum, and the residue triturated with a little chloroform at 0° and the solution filtered after 15 minutes. The product was separated by filtration and washed on the filter with chloroform, yielding a pale pink solid (29 g.), m. p. 160—165° (decomp.). Recrystallisation from chloroform (charcoal) yielded the heptanitro-compound (22 g.), m. p. 171—172° (decomp.) (Found : C, 26·5; H, 1·65; N, 21·7%).

p-*Xylylene Di-iodide*.—This was prepared from the dichloride by double exchange with sodium iodide in acetone solution, the dichloride having been made by chloromethylation of benzyl chloride (Stephen, Short, and Gladding, *J.*, 1920, **117**, 510; Quelet, *Bull. Soc. chim.*, 1933, **53**, 222). Recrystallised from benzene–ethanol, the di-iodide had m. p. 179·5—180° (Found : C, 26·9; H, 2·0. Calc. for $C_8H_8I_2$: C, 26·8; H, 2·2%). Grimaux (*Compt. rend.*, 1870, **70**, 1365; *Annalen*, 1870, **155**, 341) gives m. p. 170°; Finkelstein (*Ber.*, 1910, **43**, 1532), m. p. 174°.

1 : 4-*Bis*-2′ : 2′ : 2′-*trinitroethylbenzene*.—*p*-Xylylene di-iodide (5 g.) was suspended in dry ether

(100 c.c.) and 27 c.c. of a solution of the silver salt of trinitromethane (containing 303·5 g. per l., in ether) were added slowly. After 2 hours' stirring and a further 15 hours' standing, the silver iodide (7 g. Calc.: 6·6 g.) was filtered off, the filtrate washed with water, dried, and desolvated at 30°/20 mm.; the pale yellow semi-solid product was triturated with a little chloroform on a sintered-glass filter, yielding a solid (0·6 g.), m. p. *ca.* 165° (decomp.). Recrystallisation from chloroform yielded white needles of the *hexanitro*-compound, m. p. 190° (decomp.) (Found: C, 29·7; H, 2·3; N, 20·6. $C_{10}H_8O_{12}N_6$ requires C, 29·7; H, 2·0; N, 20·8%).

ωω'ω''-Tri-iodomesitylene.—*ωω'ω''*-Tribromomesitylene (m. p. 98—99°; 1·5 g.) was added to a solution of sodium iodide (3·0 g.) in acetone (30 c.c.); after 30 mins.' heating under reflux, most of the acetone was distilled off, and the residue washed with water and dried, yielding *ωω'ω''-tri-iodomesitylene* (2·1 g.), m. p. 131—133°; crystallised from benzene, needles, m. p. 133° (Found: C, 22·6; H, 1·9. $C_9H_9I_3$ requires C, 22·1; H, 1·9%).

1 : 3 : 5-*Tris*-2' : 2' : 2'-*trinitroethylbenzene.*—*ωω'ω''*-Tri-iodomesitylene (5·5 g.) was suspended in ether (100 c.c.) and 34 c.c. of a solution containing 287 g. of the silver salt of trinitromethane per l. of ether were added fairly rapidly. After 2 hours' stirring, the product was allowed to stand overnight. The silver iodide (7·3 g. Calc.: 7·8 g.) was filtered off, and the solution washed with water to remove unchanged silver nitroform [the amount of which was determined by conversion into silver chloride (1·3 g.), showing that the reaction was probably about 80% complete]. The ethereal solution was dried and desolvated at 30° in a vacuum, yielding a brown oil mixed with crystals. Trituration with chloroform yielded a white solid (550 mg.), m. p. 198—200° (decomp.). Two crystallisations from chloroform yielded the required *nitro*-compound (250 mg.), m. p. 205—206° (decomp.) (Found: C, 25·4; H, 1·72; N, 22·23. $C_{12}H_9O_{18}N_9$ requires C, 25·4; H, 1·59; N, 22·22%).

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233. *The Reaction of Benzoic Anhydride with Aromatic Compounds Catalysed by Boron Trifluoride.*

By P. H. GIVEN and D. LL. HAMMICK.

Boron trifluoride catalyses the interaction in nitrobenzene solution of benzoic anhydride with aromatic compounds to give ketones. Phenyl 1-naphthyl ketone, phenyl 2-hydroxy-1-naphthyl ketone, and phenyl 2-thienyl ketone are formed by reaction of the acid anhydride with naphthalene, 2-naphthyl methyl ether, and thiophen respectively. The same catalyst is effective in the Fries rearrangement of 2-naphthyl benzoate.

IN 1939—1940 we initiated a programme of work on the acylation of aromatic compounds with benzoic and other anhydrides in the presence of boron trifluoride, but were unable to complete it. We therefore record here the results of the work as far as we were able to carry it.

Meerwein and Vossen have reported (*J. pr. Chem.*, 1934, **141**, 149) the interaction of acetic anhydride with benzene and other aromatic compounds in the presence of boron trifluoride to give aryl methyl ketones, but do not mention the use of any other acid anhydrides. Their experimental procedure involved the saturation of the mixed reactants at 0° with the catalyst, followed by warming till all the fluoride was given off again. The yield of some ketones was decreased by intermolecular condensations of the acetic anhydride to give β-diketones. Bowlus and Nieuwland (*J. Amer. Chem. Soc.*, 1931, **53**, 3835) state that benzoic and phthalic anhydrides (in an unspecified solvent) do not absorb boron trifluoride, but that benzoic acid in chloroform takes up the gas, forming an insoluble complex.

We have found that benzoic and phthalic anhydrides in nitrobenzene, and the former in carbon tetrachloride and in tetrachloroethane, react with boron trifluoride, depositing solid complexes. The weight of gas taken up, after allowing for its solubility in the solvent, was approximately equivalent to 2 moles of BF_3 per mole of anhydride.

For our acylation experiments we chose nitrobenzene as solvent, on the grounds that the reaction presumably resembles the Friedel–Crafts reaction in being ionic in nature (see Linstead, *Ann. Reports*, 1937, 251; Price and Ciskowski, *J. Amer. Chem. Soc.*, 1938, **60**, 2499), and therefore should proceed most readily in a solvent of high dielectric constant.

By reaction of benzoic anhydride with thiophen we obtained a 40% yield of phenyl 2-thienyl ketone; a dirty residue, non-volatile in steam, was also formed. 2-Naphthyl methyl ether gave 55% of phenyl 2-hydroxy-1-naphthyl ketone; complete demethylation occurred.

Phenyl naphthyl ketone (77% crude product) was obtained by reaction of benzoic anhydride with naphthalene; after three crystallisations, substantially pure phenyl 1-naphthyl ketone was obtained (about 60%). Price and Ciskowski (*loc. cit.*) in the reaction of benzyl alcohol with naphthalene in the presence of boron trifluoride, also found the 1-isomer to predominate.

It was found that (under the conditions used in the benzoylations) boron trifluoride catalysed the Fries rearrangement of 2-naphthyl benzoate; a 34% yield of pure phenyl 2-hydroxy-1-naphthyl ketone was obtained.

In order to confirm the reasoning which led to the choice of nitrobenzene as solvent for the reaction mixture, an attempt was made to acylate naphthalene with benzoic anhydride in carbon tetrachloride solution. Under the same conditions as were used in the reaction in nitrobenzene only 4% of crude phenyl naphthyl ketone was obtained. Benzoic acid in reaction with naphthalene and boron trifluoride in nitrobenzene solution gave no phenyl naphthyl ketone.

The procedure used here appears to be unnecessarily vigorous for the benzoylation of reactive substances such as thiophen, as is shown by the formation of tarry by-products. The benzoylation of naphthalene by this method gives a rather higher yield of phenyl 1-naphthyl ketone, and the product is less contaminated with the 2-isomer than that of the Friedel–Crafts reaction of benzoyl chloride with naphthalene, catalysed by aluminium chloride (see, for example, Caille, *Compt. rend.*, 1911, **153**, 393); the necessary time of reaction is less (24 hours as against 3 days).

Experimental.

(Melting points are corrected.)

Materials.—Naphthalene, benzoic acid, and benzoic anhydride were dried in a vacuum desiccator before use. Solvents were dried with calcium chloride and redistilled. Boron trifluoride was prepared by the method of Krause and Nitsche (*Ber.*, 1921, **54**, 2786). A mixture of boric oxide, potassium borofluoride, and concentrated sulphuric acid was heated slowly from 135° to 250°. The gas was passed through a spray trap, but was not purified in any other way.

Absorption of Boron Trifluoride by the Reactants.—Experiments were carried out in test tubes fitted with side tubes. These, with inlet tube, rubber connections and clips were weighed empty and with the liquid before and after absorption. The liquid was cooled in ice during absorption. Absorption was allowed to proceed to constant weight. These experiments were made primarily to determine whether the acid anhydrides did or did not absorb boron trifluoride, and high accuracy is not claimed.

The data are presented in the Table. In column 4 the solubility of the gas in the solvent or solution is given in g. per 100 g. of solvent. In column 5 the molar ratio, boron trifluoride to benzoic acid or anhydride, is given.

Absorption of Boron Trifluoride.

Solute.	Solvent.	Wt. of solute per 100 g. of solvent.	Solubility, g./100 g.	Ratio, moles BF_3/ moles acid or anhydride.
None.....	Nitrobenzene	—	17·6	—
None.....	Tetrachloroethane	—	9·8	—
Benzoic anhydride	Nitrobenzene	12·6	24·4	1·8
Benzoic anhydride	Tetrachloroethane	7·87	15·0	2·2
Phthalic anhydride	Nitrobenzene	10	26·3	1·9

Benzoylation Experiments.—The reactants and solvent were placed in a three-necked flask, which was fitted with an inlet tube, mechanical stirrer, and calcium chloride tube. The stirrer was of the glass link type, and was run very fast so as to break up the surface of the liquid. A mercury-sealed stirrer was used in some experiments, but a simple well-fitting glass sleeve was found quite satisfactory. The inlet tube was bent so that the gas was delivered in the liquid, directly under the stirrer. An excess of boron trifluoride (3—5 moles per mole of benzoic anhydride) was passed in the course of 1—2 hours according to the scale of experiment. During absorption of boron trifluoride the flask was cooled in ice. After absorption, the reaction mixture was stirred and kept at 0° for 3—4 hours, and then left, while slowly warming to room temperature, for a further 18 hours. It was then shaken with dilute sodium hydroxide solution, and the solvent and any excess reactants were removed in steam. The product was obtained either from the steam distillate or from the residue by extraction.

Phenyl 2-thienyl ketone. Benzoic anhydride (2 g.) and thiophen (1 c.c.) in nitrobenzene (12 g.) were treated with excess of boron trifluoride, and the product was worked up as above. The ketone distilled in steam after the solvent had been removed; it was extracted from the distillate with ether and dried, and the ether was removed; 0·7 g. of brownish crystals was obtained. After 2 crystallisations from light petroleum (b. p. 60—80°) the compound had m. p. 52°.

Phenyl 2-hydroxy-1-naphthyl ketone from 2-naphthyl methyl ether. Benzoic anhydride (4 g.) and 2-naphthyl methyl ether (2·5 g.) in nitrobenzene (18 g.) were treated with excess of boron trifluoride as above. From the residue of the steam distillation, 2·5 g. (70%) of crude ketone were obtained, completely soluble in warm sodium hydroxide solution. Crystallised from ligroin and twice from 60% alcohol, it gave fine yellow needles, m. p. 140—140·5°.

Phenyl 1-naphthyl ketone. (*a*) Benzoic anhydride (22·6 g.), naphthalene (12·8 g.), and nitrobenzene (140 c.c.) were treated with about 23 g. of boron trifluoride (*i.e.*, about 3 moles per mole of benzoic anhydride). From an ether extract of the residue from the steam distillation, 19 g. (77%) of crude

phenyl naphthyl ketone were obtained. A solution of 0·3 g. in 1 c.c. of benzene gave no precipitate after being boiled for 2 minutes and kept for 15 hours with 0·2 g. of picric acid in 1 c.c. of benzene (the 2-isomer gives an insoluble picrate in benzene, the 1-isomer none, and a mixture can be separated by virtue of this fact; see Perrier and Caille, *Compt. rend.*, 1908, **146**, 769). The remainder of the crude product was crystallised 3 times from dilute alcohol, with charcoal; m. p. 73—74° (Perrier and Caille, *loc. cit.*, give 76°).

(*b*) Naphthalene (4·3 g.) and benzoic anhydride (7·5 g.) in carbon tetrachloride (75 c.c.) were treated with excess of boron trifluoride; a copious white precipitate was thrown down. About 2·8 g. of unchanged naphthalene were found in the steam distillate. From the residue 0·3 g. (about 4%) of crude phenyl naphthyl ketone was obtained.

Attempted reaction of benzoic acid with naphthalene. Benzoic acid (5 g.) and naphthalene (5 g.) in nitrobenzene (65 c.c.) were treated with boron trifluoride as above. The materials were recovered substantially unchanged, and no phenyl naphthyl ketone was detected.

Fries Rearrangement of 2-Naphthyl Benzoate.—Naphthyl benzoate (7 g.) in nitrobenzene (65 c.c.) was treated with a large excess (about 15 g.) of boron trifluoride as above. The residue from the steam distillate was made strongly alkaline, and filtered hot from some black solid. The filtrate was made acid and filtered again. The residue on the filter was crystallised twice from dilute alcohol with the addition of charcoal. The product was phenyl 2-hydroxy-1-naphthyl ketone (2·4 g., 34%), m. p. 140·5—141°.

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234. *The Reduction of Oxides by Hydrogen and Carbon Monoxide.*

By W. E. GARNER.

The previous investigations on the heats of adsorption of hydrogen, carbon monoxide, oxygen, and carbon dioxide on ZnO, $MnO_{1\cdot5}$, Cr_2O_3 and their mixtures have been summarised. These oxides are semi-conductors and there is considerable mobility of ions in the oxide lattice at the temperature of reduction. The adsorption at room temperature takes place on a surface which may be the result of an equilibrium set up in a lattice defect structure at higher temperatures.

Reversible chemisorption of carbon monoxide occurs on metal-rich oxides with negative holes, and irreversible chemisorption on oxides with positive holes. The two types of chemisorption are not readily interconvertible. The reversible adsorption of carbon monoxide on zinc oxide, and the adsorption of carbon dioxide on the oxides of the transition elements occur without appreciable activation energy. It is suggested that when carbon monoxide is adsorbed irreversibly, there is set up a resonating system involving the *S* and *D* shells of the transition element. This system is moved in the direction of the carbonate ion, when the stoicheiometric quantity of oxygen is adsorbed on the surface. The ease with which the carbonate ion is dissociated is thus determined by the number of unpaired electrons in the *D* and *S* shells of the transition element.

INVESTIGATIONS on the reduction of metallic oxides by hydrogen and carbon monoxide have shown that the reaction proceeds through a number of intermediate stages to yield hydroxides and carbonates which decompose to produce the lower oxide or metal (Garner and Kingman, *Trans. Faraday Soc.*, 1931, **27**, 322; Garner and Veal, *J.*, 1935, 1436, 1487; Dowden and Garner, *J.*, 1939, 894; Garner and Ward, *J.*, 1939, 858; Ward, following paper). The processes which precede the evolution of water or carbon dioxide include (*a*) van der Waals adsorption, which is specially predominant at low temperatures, and also (*b*) several types of chemisorption. The rate of chemisorption on oxides increases rapidly with increase of temperature, which led Taylor (*J. Amer. Chem. Soc.*, 1931, **53**, 578) to designate this type of process as " activated " adsorption. The heats of chemisorption of carbon monoxide and hydrogen on a number of oxides range from 15 to 70 k.-cals./mol., according to the oxide. It is found that if the heat of adsorption is below 20 k.-cals./mol., the gas can be desorbed unchanged on raising the temperature, but when the heat is greater than this value, the adsorption is usually irreversible, in the sense that, on warming, carbon dioxide or water is evolved. The results have been obtained on oxides which are reducible with difficulty. They may, however, be capable of application to easily reduced oxides, where the various stages in the reaction may proceed too quickly for them to be readily isolated from one another.

Chemisorption of Carbon Monoxide and Hydrogen.—In Table I are summarised the heats of adsorption of the two gases on a number of oxides at room temperature. On zinc oxide, carbon monoxide is adsorbed reversibly and carbonates are not formed, the activation energies and heats of reaction being unfavourable for the formation of carbonates in this case. For a mixture of zinc and chromium oxides, the adsorption of hydrogen or carbon monoxide is partly reversible and partly irreversible, the proportion of the two types of chemisorption depending on the state

TABLE I.

Heats of adsorption (in k.-cals./mol.) of CO *and* H_2 *on oxidised and on reduced surfaces.*

Substance.	H_2. Reduced.	H_2. Oxidised.	CO. Reduced.	CO. Oxidised.	Remarks.
ZnO	No appreciable adsorption		20	18 → 13	Reversible desorption of CO at room temp.
Cr_2O_3	36	72	29 → 22	28 → 12	Hydrogen very difficult to remove, even by long treatment at 450°; CO evolved as CO_2 at 70—400°.
$MnO_{1\cdot5}$	44	30	67	62	
ZnO, Cr_2O_3	13 → 10	48 → 13	15 → 11	44 → 16	Partial desorption of CO and H_2 at room temp.
$MnO_{1\cdot5}, Cr_2O_3$ ...	No appreciable adsorption		33	47	CO not desorbed at room temp.

of reduction of the oxide. On heating the oxide on which hydrogen or carbon monoxide is reversibly chemisorbed to 100—200°, the gas is evolved unchanged. The pressure rises to a maximum and then falls to zero. On further heating to 400° the gas is evolved as water or carbon dioxide respectively. It is clear that the direct conversion from reversible to irreversible chemisorption does not occur, since the surface reaction is hindered by a high potential energy barrier which is greater than the heat of desorption of the gas (see Fig.). This may be due to the two states of adsorption taking place on different centres. For the other oxides quoted in Table I, the adsorption is, for the most part, irreversible.

Formation of Carbonates.—Information relevant to the formation of carbonates on the surface of the oxides is given in Table II. The oxides were treated with oxygen at 450°, then evacuated and cooled to room temperature. Measurements were made of the heats of adsorption of carbon monoxide, oxygen, and carbon dioxide, and of mixtures of carbon monoxide and oxygen.

When the carbon monoxide is adsorbed irreversibly, carbon dioxide can be liberated on raising the temperature, but it is difficult to desorb this gas at room temperature. On the other hand, if carbon dioxide is adsorbed on the oxide, the heat of formation of the carbonate is of the order of 20 k.-cals., and the gas can be usually desorbed at room temperature, at a rate given by the Polanyi–Wigner equation, $r = \nu . Ne^{-Q/RT}$, where Q is the heat of adsorption, N is the number of molecules adsorbed on 1 cm.^{2} of the surface, and $\nu = 10^{13}$ sec. The absence of appreciable activation energy in the formation and dissociation of carbonates is in agreement with the conclusions of Zawadzki and Bretsznajder (*Z. Elektrochem.*, 1935, **41**, 215) and Spencer and Topley (*J.*, 1929, 2633). It is, however, clear that when carbon monoxide is adsorbed on an oxide, the product differs in some way from the carbonate formed from carbon dioxide.

TABLE II.

Heats of adsorption (in k.-cals./mol.) of CO *and* $\frac{1}{2}O_2$ *on oxidised surface.*

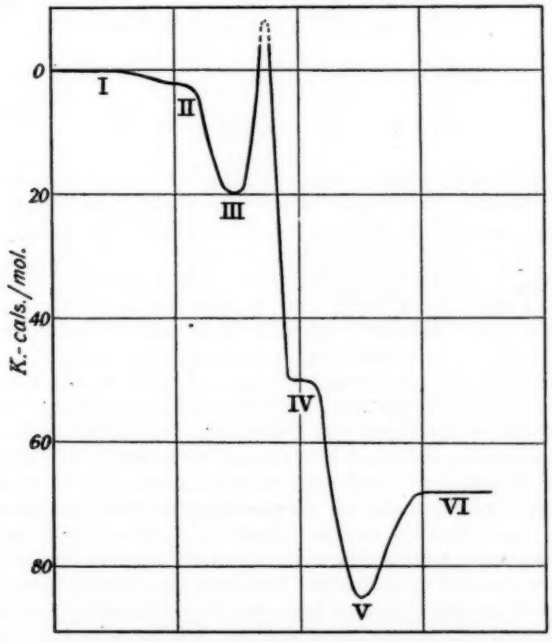
1. Substance.	2. CO.	3. $\frac{1}{2}O_2$ after CO.	4. CO + $\frac{1}{2}O_2$.	5. CO_2.	6. Total heat.	7. $\frac{1}{2}O_2$ on reduced surface.
ZnO	18	—	—	13	—	—
Cr_2O_3	29	55	84 †	18	66	40—50
	61 *	38 *	—	—	—	—
$MnO_{1\cdot5}$	67	24	82	23	68(59)	31
ZnO,Cr_2O_3	44(18)	22	66	15	51	22
$MnO_{1\cdot5},Cr_2O_3$ ...	47	39	85	20	65	52 * 19

* Oxide containing hydrogen as hydroxide. † Calculated.

The surface after adsorption of carbon monoxide (col. 2) is, however, unsaturated with respect to oxygen, and a quantity of oxygen can be taken up with the liberation of the heats shown in col. 3. These heats are quite large and depend on the previous history of the oxide as well as on its nature. For Cr_2O_3 the heats are lower if hydrogen is present in the oxide. The observations made with $MnO_{1\cdot5},Cr_2O_3$ are instructive. The adsorbed carbon monoxide cannot be removed by evacuation at room temperature, but after the adsorption of oxygen or after the adsorption of CO + $\frac{1}{2}O_2$ (col. 4), carbon dioxide is liberated on evacuation with a heat of desorption equal to the heat of adsorption of carbon dioxide (col. 5). In order to produce a carbonate from carbon monoxide with the same properties as that formed from carbon dioxide,

it is necessary to reoxidise the surface with the stoicheiometric quantity of oxygen. It will be noted that the total heats given in col. 6 correspond in most cases with the heat of the reaction, $CO + \frac{1}{2}O_2 \longrightarrow CO_2$, which provides a good check on the accuracy of the measurements.

Formation of Hydroxides.—The position with regard to the formation of hydroxides is not so clear, since the results at room temperature were not sufficiently complete. " Activated " adsorption of hydrogen does not readily occur on some of the oxides at room temperature. It was shown, however, in a number of cases that the surface reduced with hydrogen was not unsaturated to the same extent as with carbon monoxide. Also, the hydrogen adsorbed irreversibly is so tightly held that it is difficult to remove it completely without sintering the oxide. Thus no information could be obtained with regard to the heat of desorption of water. For Cr_2O_3, the hydrogen cannot be completely removed, even at 450°. It can, however, be removed in the course of the reduction by carbon monoxide, which mobilises the adsorbed hydrogen. The residual hydrogen in the case of Cr_2O_3 is found to increase materially the heat of adsorption of carbon monoxide.



The reduction of oxides by carbon monoxide.

Energy Levels.—The energy levels formed during the reduction of the oxides are set out schematically in the figure. This only gives a very approximate representation of the results of Table II, since the position of the levels varies with the oxide. The levels from left to right are: I, $CO + \frac{1}{2}O_2$; II, van der Waals adsorption of CO; III, reversible chemisorption of CO; IV, irreversible adsorption of CO, leading to an unsaturated surface; V, adsorption of $CO + \frac{1}{2}O_2$; and VI, carbon dioxide. There is an activation energy between II and III and carbon monoxide may be desorbed unchanged on raising the temperature if this activation energy is greater than the heat of desorption. This is the case for the adsorption of carbon monoxide on ZnO,Cr_2O_3. The overall change from I to VI is the conversion of carbon monoxide and oxygen into carbon dioxide.

Lattice Irregularities.—These oxides belong to the class of semiconductors, the electrical conductivity being due to a defect or excess of some ion in the lattice. Zinc oxide dissolves zinc, giving negative holes in the lattice. Oxides of manganese give a series of partially miscible solid solutions of MnO, Mn_3O_4, and Mn_2O_3, which can only be produced at the expense of some lattice irregularity. In this case, oxygen is in excess, which probably gives rise to positive holes in the lattice. It is thus similar to the cuprous oxide, which has been thoroughly investigated by Wagner (cf. Mott and Gurney, " Electronic Processes in Ionic Crystals ", 1940), who shows that there is considerable mobility of the ions at high temperatures. On removal of oxygen by

reduction, negative holes will be produced on the surface, and if the temperature is sufficiently high, these negative holes will migrate into the interior of the lattice, their place on the surface being taken by oxygen ions. The surface reduction of oxides might therefore at sufficiently high temperature lead to a movement of oxygen from the interior of the lattice to the surface.

A phenomenon of this type possibly occurs at 450°, when the oxides are undergoing reduction. The extent to which the reduction occurs at this temperature and the quantities of gas which can be absorbed on the reduced surface are shown in Table III.

TABLE III.

Reduction of surfaces of oxides.

Substance.	Wt., g.	Gas used in reduction.	Vol. of gas used up at 400—450°.	Gases adsorbed on reduced surface at saturation, in c.c. at room temp.			Remarks.
				H_2.	CO.	O_2.	
ZnO,Cr_2O_3	14·8	H_2	200	3·0	1·4	9·0	
ZnO	6·0	H_2	3 c.c./hr.	V. small	0·35	—	Zn volatilises on reduction
$MnO_{1·5}$	11·2	CO	64	—	2·0	—	
		H_2	243	0·17	—	—	
Cr_2O_3	16·1	CO	57	V. small	32·3	30·0	
$MnO_{1·5},Cr_2O_3$ ...	19·7	CO	28	V. small	1·0	0·10	

If the surfaces are reduced stepwise, only a relatively slow change in the character of the surface occurs as the reduction proceeds. Thus with ZnO,Cr_2O_3 the reduction by 50 c.c. of hydrogen out of a total possible of 200 c.c. made no significant difference to the volume of hydrogen adsorbed or to its heat of adsorption at room temperature. A similar result also was obtained with $MnO_{1·5}$; the adsorption and heat of adsorption of carbon monoxide was not appreciably affected by the partial reduction of the oxide. Also, the amount of oxygen adsorbed and the heat of adsorption of oxygen on Cr_2O_3 only increases slowly as the surface is reduced. The amount of oxygen adsorbed by manganous–chromic oxide is only slightly affected by the reduction process. As oxygen is removed from the surface during the reduction, there is evidently some compensating factor which keeps the properties of the surface unchanged. This may well be the diffusion of oxygen ions from the lattice to the surface.

At room temperature the mobility of the oxygen ions within the lattice is probably very low, so that the oxide under these conditions would be expected to be a frozen form of the equilibrium set up at higher temperatures. The adsorption of hydrogen and carbon monoxide at room temperature may therefore take place on lattice irregularities caused by the establishment of equilibrium in a lattice defect structure at higher temperatures. The bearing of lattice defects on the reduction of oxides and for catalysis generally has not yet received much attention, and no researches appear to have been directed specifically to clear up this point.

Activation Energy during the Reduction of Oxides.—Carbon monoxide is adsorbed on oxide surfaces in two ways, (1) reversibly and (2) irreversibly. The first type occurs on ZnO, on ZnO,Cr_2O_3, and only to a small extent on the other oxides. On zinc oxide the heat of adsorption is 18 k.-cals. and the gas can be completely desorbed at room temperature within 20 minutes. The rate of desorption is given by $N\nu e^{-E/RT}$, where N = number of adsorbed molecules per cm.^{2}, $\nu = 10^{13}$ as a maximum value, and E = the energy required to evaporate the molecule from the surface. Calculation shows that E is approximately the same as the heat of adsorption within a few calories. The reversible adsorption is thus not appreciably activated.

On ZnO,Cr_2O_3, both types of adsorption occur, but the passage from reversible to irreversible adsorption does not readily occur on the surface. On heating, carbon monoxide first evaporates and then condenses to give an adsorption complex from which carbon dioxide can be liberated. It is very probable, therefore, that different centres are involved in the two types of adsorption process.

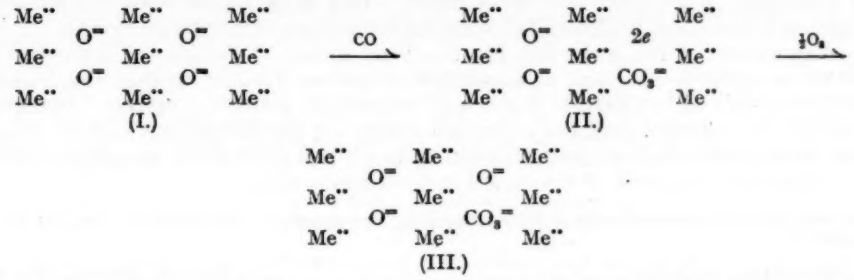
On oxides of the transition elements and their mixtures, carbon monoxide reacts with two oxygen ions or atoms on the surface to give $CO_3^{=}$ ions, liberating two electrons :

$$(1)\quad CO + 2O^{=} \longrightarrow CO_3 + 2e$$

The surface has become unsaturated with respect to oxygen, which can be added in stoicheiometric quantities, *viz.*, $\frac{1}{2}O_2$ to each CO :

$$(2)\quad \tfrac{1}{2}O_2 + 2e \longrightarrow O^{=}$$

The process is shown schematically below for a bivalent metal ion.



The following qualitative picture can be given in explanation of the experimental results. The electrons set free in (II) will be held in the neighbourhood of the carbonate ion. They will possibly be accommodated in the *S* or *D* shells of the transition element,* which, together with the $CO_3^{=}$ ion, can form a resonating system :

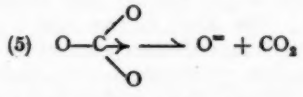
$$(3)\quad CO + 2O^{=} + 2Me^{\cdot\cdot} \rightleftharpoons CO_3 + 2Me^{\cdot}$$

The addition of $\frac{1}{2}O_2$ in (III),

$$(4)\quad \tfrac{1}{2}O_2 + 2Me^{\cdot} \longrightarrow O^{=} + 2Me^{\cdot\cdot}$$

will have the effect of moving the resonating system in (3) to the right, *i.e.*, in the direction of the formation of $CO_3^{=}$ ion, which would explain the observation that CO_2 is evolved more readily from state (III) than from state (II).

The carbonate ion can be dissociated to give carbon dioxide. Measurements of the rates of desorption show that within a few calories the activation energy is the same as the heat of adsorption. The process of dissociation involves the displacement of the carbon atom as in (5), and the transference of the two electrons to an oxygen atom and the metal ions associated



with it in the lattice. An activation energy might be expected for this step, but it may be small,† especially if there is some choice among the levels of the *D* and *S* shells of the transition element, in the formation of the bond between the oxygen ion and the surrounding metal ions. If there is a broad band of electronic levels in the shells of the transition element, which are suitably placed with respect to the levels of the oxygen and carbonate ions, then the electron transfer reactions (3)—(5) would be facilitated. The effectiveness of the transition metals for catalysis generally may depend on a suitable distribution of the electron levels in the catalyst.

When carbon monoxide is adsorbed reversibly on zinc oxide, the surface does not become unsaturated with respect to oxygen, and no additional oxygen can be adsorbed after carbon monoxide. This is in accord with the view that reversible and irreversible adsorption of carbon monoxide occur on different centres.

Conclusions on the Reaction of Carbon Monoxide with Oxides.—It has been demonstrated that reversible adsorption of carbon monoxide occurs on metal-rich oxides with negative holes in the lattice, and irreversible adsorption on oxides defective in metal ion with positive holes. The two types of adsorption are not readily inter-convertible and probably occur on different types of centre. Reversible chemisorption may take place on sites where electrons can be donated to the adsorbed molecule, and irreversible adsorption on sites which can abstract electrons from the molecule. The reversible adsorption is not appreciably " activated ".

It is suggested that the resonating system $CO + 2O^{=} + 2Me^{\cdot\cdot} \rightleftharpoons CO_3^{=} + 2Me^{\cdot}$ may play an important part in the irreversible adsorption. The carbon monoxide is held in an intermediate state on the way to a $CO_3^{=}$ ion. This system will move to the right if the number of unpaired electrons in the shells of the metal ion is increased, so that the extent to which the

* The transition elements are most effective as catalysts when their magnetic susceptibility is highest, indicating that the unpaired electrons in the *D* shell play an important part in heterogeneous catalysis (Hüttig, *J. Amer. Chem. Soc.*, 1935, **57**, 2470; Hofer, Peebles, and Dieter, *ibid.*, 1946, **68**, 1953; Selwood, Hill, and Boardman, *ibid.*, p., 2055).

† I am indebted to Dr. F. C. Frank for this suggestion.

carbonate ion is formed can be increased by the adsorption of oxygen simultaneously with carbon monoxide, $\frac{1}{2}O_2 + 2Me^{\cdot} \longrightarrow O^{=} + 2Me^{\cdot\cdot}$. This is in accord with the fact that the carbonate ion is more readily dissociated when the surface is saturated with oxygen.

The dissociation of the carbonate ion has been shown to possess an activation energy approximately equal to the heat of adsorption of carbon dioxide, so that the formation of carbonate ions from carbon dioxide requires no appreciable activation energy. In explanation of this fact, it is suggested that the activation energy for the dissociation may be small if the electronic levels of the shells of the metal ions lie in a broad band which is suitably placed with respect to the electronic levels of the oxygen and carbonate ions.

I am indebted to Imperial Chemical Industries Ltd. for a grant for the purchase of apparatus used in these researches.

THE UNIVERSITY, BRISTOL. [*Received, December 8th*, 1946.]

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235. *Heat of Adsorption of Gases on Manganous–Chromic Oxide at Room Temperature.*

By T. WARD.

Measurements have been made of the heats of adsorption of carbon monoxide, carbon dioxide, and oxygen. Carbon monoxide is irreversibly adsorbed, giving carbon dioxide on rise of temperature. The surface, after the addition of carbon monoxide, is unsaturated with respect to oxygen. The evolution of carbon dioxide is facilitated after the unsaturation has been removed, and carbon dioxide can be desorbed with a heat of desorption equal to the heat of adsorption of carbon dioxide. The adsorption of carbon dioxide is not " activated ".

THIS investigation is a continuation of a series of experiments on the heats of adsorption of carbon monoxide, carbon dioxide, oxygen, and hydrogen on the metallic oxides, ZnO, $MnO_{1\cdot5}$, and Cr_2O_3, and the changes in adsorptive properties that occur on mixing two of the oxides (Garner and Veal, *J.*, 1935, 1436, 1487; Garner and Kingman, *Trans. Faraday Soc.*, 1931, **27**, 322; Dowden and Garner, *J.*, 1939, 894; Garner and Ward, *ibid.*, p. 858). In the present work, a study has been made of the heats of adsorption of the above gases on the fully oxidised, reduced, and partly reduced surfaces of manganous–chromic oxide. Particular attention has been paid to the formation of carbonates from carbon monoxide and oxygen, and from carbon dioxide.

Although the properties of Cr_2O_3 and MnO_2 as promoters are well known, little attention appears to have been paid to the study of adsorption on the mixed oxides. Taylor and Williamson (*J. Amer. Chem. Soc.*, 1931, **53**, 2168) have shown that over the range — 78·5° to 144° there are two forms of adsorption of hydrogen and carbon monoxide. At — 78·5° hydrogen was adsorbed molecularly with a heat of 1·9 k.-cals./mol., as calculated from adsorption isotherms. At 300—400°, the heat of adsorption of hydrogen was ~20 k.-cals. Only qualitative results were obtained with carbon monoxide.

EXPERIMENTAL.

Preparation of the Oxide.—Manganous ammonium chromate was prepared by the method of Taylor and Williamson (*loc. cit.*) by the interaction of manganous nitrate and ammonium chromate, the solution being titrated until just neutral with ammonia and then filtered. The precipitate was washed thoroughly with ammonium nitrate solution, then with distilled water, and finally dried. It was now oxidised at 400° in a stream of oxygen for 48 hrs., a black amorphous powder being formed. The powder was unsuitable for use in the type of calorimeter employed; hence, it was pressed into small tablets by means of a pastel press, these tablets being then cut into squares 0·1 mm. in size. It was finally treated *in situ* with oxygen at 400°. No information concerning the *X*-ray structure of the spinel could be obtained.

Specific Heat of the Oxide.—This was determined by the method employed by Garner and Randall (*J.*, 1924, **125**, 881). The average value for the determination was 0·166 cal./deg.

Calorimeter.—This was of the type 1f (Garner and Veal, *loc. cit.*), but with the slight alterations mentioned by Garner and Ward (*loc. cit.*), where the details of the method of measurement are given. The weights of the materials used were, platinum 1·6506 g., Pyrex 2·4023 g., oxide 19·680 g., and the specific heats 0·0314, 0·20, and 0·166 cal./deg. respectively. These values gave a water equivalent of the calorimeter of 3·800 cals./deg.

The calibration of the calorimeter was carried out by noting the change in temperature by a standardised Beckmann thermometer when the temperature of the calorimeter fluid was altered by the addition of either ice or hot water, and at the same time recording photographically the e.m.f. of the thermocouple on a Z.c. Kipp and Zonen galvanometer. The sensitivity was 15 cm. per degree.

A preliminary series of experiments showed that the heat conductance of the catalyst was good; the admission of helium as a diluting gas and the mixing of the oxide with gold wire (Garner and Dowden, *loc. cit.*) were therefore unnecessary. The cooling correction was determined after saturating the oxide with oxygen, carbon dioxide, etc., at pressures of 10^{-4}—10^{-3} cm., allowing the system to come to equilibrium, and then reducing the temperature of the calorimeter by 1° or 2°. The change in e.m.f. of the thermocouple was recorded, and the loss of temperature per minute for a difference of temperature of 1° between the calorimetric fluid and the thermocouple was obtained for every minute up to the 20th. The values obtained were, 1—6 mins., 0·020°; 6—10 mins., 0·018°; 10—15 mins., 0·016°; 15—20 mins., 0·015°. These values were independent of the gas used, and held over a range of pressures from hard vacuum to 10^{-2} cm. In the following experiments the pressure was not allowed to rise above 10^{-2} cm.

There was no drift with time in the values of the heats of adsorption, except in a few experiments where slow reactions occurred, showing that a uniform distribution of gas was attained throughout the calorimeter.

For most of the work the oxide was reduced by carbon monoxide at 400°. Hydrogen was not employed in the reduction until the end of the experiments, in order to avoid contamination of the solid with hydrogen in the initial experiments.

Adsorption of Oxygen.—28 C.c. of carbon monoxide were required to reduce the surface, and beyond this point the reduction was so slow as to be noticeable only after several days. The extent of the reduction was determined by freezing out and measuring the volume of the carbon dioxide formed. The results for the heats of adsorption on the oxidised, reduced, and partly reduced surface are given below. The last value was obtained on a surface reduced with hydrogen. The partly reduced surface gave lower values for the heat of adsorption than either the fully oxidised or the fully reduced surface.

Reduction of surface (c.c. of CO).	Oxygen adsorbed (c.c.).	Heat of adsorption (k.-cals.).	Reduction of surface (c.c. of CO).	Oxygen adsorbed (c.c.).	Heat of adsorption (k.-cals.).
0	0·2	22 *	18	0·03	− 4·6 †
4	0·045	− 6·6 †	28	0·09	+19·1
8	0·10	− 6·0 †	30 (H_2)	0·08	+52

* After oxidation at 400°.

† The adsorption on the partially reduced surface was abnormal. The galvanometer showed an immediate absorption of heat, recorded above, followed by a slow positive evolution. The negative values were not due to the presence of temperature gradients in the oxide, since the addition of helium before the experiments gave no change in temperature.

Adsorption of Carbon Dioxide.—The oxidised surface adsorbed 1·8 c.c. of carbon dioxide at a pressure of 10^{-3} cm. For the measurements of heats of adsorption, the gas was admitted 0·6 c.c. at a time and a heat of 20 k.-cals. was obtained for the first admission and 14 k.-cals. for the second. All of the gas could be desorbed on evacuation at room temperature, and the heat of desorption after the first admission gave 19 k.-cals. The rate of desorption was measured, and the Polanyi–Wigner equation, rate $= N\nu e^{-Q/RT}$, applied, the symbols are as defined in the preceding paper. If Q is calculated from the rate, a value of 22 k.-cals. is obtained for the heat of desorption. On the fully reduced surface the heat of adsorption of carbon dioxide was lower: 0·5 c.c. gave 14 k.-cals. The heat of desorption of this gas was 13 k.-cals. These results show that very little activation energy is needed for the adsorption of carbon dioxide, in agreement with the majority of the results in previous papers.

Adsorption of Hydrogen.—No hydrogen could be adsorbed on the oxidised or reduced surfaces at room temperature, although at 400° the catalyst could be readily reduced. Neither was there any appreciable adsorption of hydrogen when the gas was mixed with oxygen. This is in agreement with the experiments of Taylor and Williamson (*loc. cit.*), who did not obtain appreciable "activated" adsorption of hydrogen below 100°.

Adsorption of Carbon Monoxide, followed by Oxygen.—The carbon monoxide was adsorbed on the oxidised surface, and oxygen admitted subsequently to the same surface. The quantity of oxygen adsorbed was always less than the stoicheiometric proportion given by the ratio $CO : \frac{1}{2}O_2$. Three series were carried out:

Gas.	C.c. adsorbed.	Heat of adsorption (k.-cals.).	Total (k.-cals.).	Gas.	C.c. adsorbed.	Heat of adsorption (k.-cals.)	Total (k.-cals.).
CO	0·602	46	85	CO	0·682	48	80
O_2	0·132	78		O_2	0·168	64	
CO	0·546	45	83				
O_2	0·113	76					

Carbon monoxide could not be desorbed from the oxide at room temperature until the oxygen had been adsorbed, whereupon it could be completely desorbed as carbon dioxide with a heat of 22 k.-cals. This is the same as the heat of adsorption of carbon dioxide on the oxide surface, so that it is clear that the same adsorption state has been reached from carbon monoxide and oxygen as was obtained with carbon dioxide.

If the surface was saturated previously with 1·81 c.c. of carbon monoxide, only about 0·19 c.c. of oxygen was adsorbed, with a heat of 76 k.-cals., which was the same as that given in the above table, but in this case the heat was liberated slowly and was not completely evolved until 20 mins. had elapsed. This indicates that adsorbed oxygen is undergoing a slow reaction with the surface. On desorption, the carbon dioxide was evolved at room temperature with a heat of 20 k.-cals.

A mixture of $CO + \frac{1}{2}O_2$ was admitted to the oxidised surface (0·4 and 0·8 c.c. respectively) and completely adsorbed. A heat of 85 k.-cals. was liberated, which is in agreement with the total heat

in the above table. The heat of desorption of carbon dioxide in this case was 18 k.-cals., which is within a few calories the same as the heat of adsorption of carbon dioxide.

On the surface reduced with 28 c.c. of carbon monoxide, carbon monoxide was adsorbed with a heat of 33 k.-cals. (0·7 c.c. adsorbed).

Discussion.

The measurements of the heats of adsorption on the mixed oxide, $MnO_{1\cdot5},Cr_2O_3$, and the two oxides separately do not bring to light any phenomena which might be said to characterise promoter action. The research has only been concerned with measurements at one temperature. For the study of promoter action, measurements need to be made over a range of temperatures, in order to cover adequately the range at which chemisorption occurs. At room temperature, the slight adsorption of hydrogen on the separate oxides, and negligible adsorption on the mixed oxides, make it impossible to obtain much information about promoter action in so far as the adsorption of hydrogen is concerned.

It has become evident as the work proceeded that measurements were giving information on the reduction of oxides by hydrogen and carbon monoxide. This aspect of the results will be dealt with in a separate communication. This discussion will be limited to aspects more specifically derived from the results in the present paper.

It is a striking fact that, for both manganous oxide and manganous–chromic oxide, the reduction of the surface at 400° does not materially increase the quantities of oxygen which can be taken up at room temperature. This is in marked contrast with the behaviour of ZnO,Cr_2O_3 and Cr_2O_3, where there is an increase on reduction of the quantities of oxygen adsorbed. These differences in behaviour are very probably due to differences in the mobility of the constituents of the lattice at the temperature at which the reduction is carried out. Too little is known about these movements in the case of these oxides to warrant an attempt at a very precise interpretation. The oxides belong to the semi-conductor class for which there is an appreciable electrical conductivity due to lattice defects. A possible interpretation of the results with manganous oxide and manganous–chromic oxide is that the oxygen ions are mobile at the temperature of reduction and that the effects of reduction of these oxides are made good by the diffusion of oxygen from the lattice to the surface at which reduction occurs.

When an oxide is reduced with hydrogen, it is difficult to remove the last traces of water. These materially affect the heats of adsorption, as was pointed out previously in the paper on Cr_2O_3. A hydrogen-reduced surface of manganous–chromic oxide gives a greater heat of adsorption of oxygen than a carbon monoxide-reduced surface. The heat obtained approaches that given when oxygen is adsorbed on a surface containing carbon monoxide. The high heat may thus be due to lattice defects caused by the presence of hydroxyl ions in the lattice.

The results obtained with carbon monoxide and carbon dioxide are perhaps of the greatest interest, since they can be interpreted unequivocally. Carbon dioxide is adsorbed on manganous oxide, manganous–chromic oxide, and chromic oxide to give carbonates without the necessity for activation energy. The heat of desorption is the same as the heat of adsorption, and the rate of desorption can be calculated from the Polanyi–Wigner equation.

When carbon monoxide is adsorbed on the oxidised surface, the product formed cannot be dissociated at room temperature, and carbon dioxide is evolved only after the temperature is raised. The surface is, however, unsaturated after the adsorption of carbon monoxide, and can take up oxygen. When the unsaturation has been removed, carbon dioxide can be desorbed by evacuation at room temperature. The same final state is produced, whether starting from carbon dioxide or from carbon monoxide, provided in the latter case that oxygen be added at the same time. This is made clear by the following data derived from the heats of adsorption :

$$\left.\begin{array}{l} 2XO + CO \longrightarrow 2XO,CO + 47 \text{ k.-cals.} \\ 2XO,CO + \tfrac{1}{2}O_2 \longrightarrow XO + XCO_3 + 38{\cdot}5 \text{ k.-cals.} \end{array}\right\} 85{\cdot}5 \text{ k.-cals.}$$

$$2XO + CO + \tfrac{1}{2}O_2 \longrightarrow XCO_3 + XO + 85{\cdot}5 \text{ k.-cals.}$$

$$\left.\begin{array}{l} CO + \tfrac{1}{2}O_2 \longrightarrow CO_2 + 68 \text{ k.-cals.} \\ 2XO + CO_2 \longrightarrow XO + XCO_3 + 20 \text{ k.-cals.} \end{array}\right\} 88 \text{ k.-cals.}$$

The agreement between the heats for the three processes shows that a carbonate is produced in the reaction of carbon monoxide and oxygen with the oxide.

The author wishes to acknowledge the receipt of a grant from Imperial Chemical Industries, Ltd., for the purchase of apparatus.

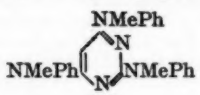
The University, Bristol. [*Received, December 8th*, 1946.]

236. *The Constitution of a By-product from the Preparation of Trichloropyrimidine from Barbituric Acid.*

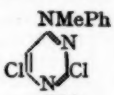
By F. E. King, T. J. King, and P. C. Spensley.

The constitution of a high-boiling crystalline by-product from the reaction between barbituric acid, phosphoryl chloride, and dimethylaniline is shown by synthesis to be 4 : 6-*dichloro*-2-N-*methylanilinopyrimidine* and not the expected 2 : 6-dichloro-4-*N*-methyl compound.

When preparing 2 : 4 : 6-trichloropyrimidine from barbituric acid by the improved method of Baddiley and Topham (*J.*, 1944, 679), using phosphoryl chloride and dimethylaniline, a crystalline by-product was isolated from the residue, after distillation of the trichloro-compound, as a fraction of b. p. 240—300°. The yield of recrystallised product averaged 5%, and it was at first believed to be a partly chlorinated barbituric acid. However, analyses indicated the structure to be that of a dichloropyrimidine containining a monomethylaniline residue, thus suggesting either 4 : 6-dichloro-2- or 2 : 6-dichloro-4-*N*-methylanilinopyrimidine as the correct constitution. The by-product was still obtained even when dimethylaniline carefully freed



(I.)



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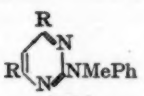

(III.)

from traces of the monomethyl compound was employed, and its formation is therefore similar to that of 2 : 4 : 6-tri-*N*-methylanilinopyrimidine (I) from trichloropyrimidine and dimethylaniline (Kawai and Miyoski, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1931, **16**, 20), in which the loss of methyl chloride from an intermediate quaternary salt is involved.

Since the action of aniline on trichloropyrimidine is presumed to give 2 : 6-dichloro-4-anilinopyrimidine (Winkelmann, *J. pr. Chem.*, 1927, **115**, 305), the constitution of the new pyrimidine was thought to be analogous. This supposition was, however, disproved when the condensation of monomethylaniline and trichloropyrimidine in ethanol gave the non-identical 2 : 6-*dichloro*-4-N-*methylanilinopyrimidine* (II). Its 2-*methylanilino*-isomer (III, R = Cl) was therefore synthesised from α-phenyl-α-methylguanidine and ethyl malonate in alcoholic sodium ethoxide solution, the intermediate N-*methylanilinodihydroxypyrimidine* (III, R = OH) giving on treatment with phosphoryl chloride a product indistinguishable from the substance under investigation.

By means of the phosphoryl chloride–dimethylaniline method, 4 : 6-*dichloro*-5-p-*chlorobenzeneazo*-2-*methylpyrimidine* has been prepared from the corresponding dihydroxypyrimidine (Lythgoe, Todd, and Topham, *J.*, 1944, 3151), but under similar conditions the 2 : 4 : 6-*trihydroxy*-5-p-*chlorobenzeneazo*-compound gave only tarry products.

Experimental.

2 : 6-*Dichloro*-4-N-*methylanilinopyrimidine*.—Methylaniline (11 g., 2 mol.) was added to a solution of trichloropyrimidine (9·2 g., 1 mol.) in ethanol (40 c.c.) at room temperature. After 3 hours the colourless product was collected and crystallised from alcohol. The *dichloromethylanilinopyrimidine* (II) separated in tiny prisms, m. p. 106—107° (Found : C, 51·7; H, 3·8; Cl, 27·8. $C_{11}H_9N_3Cl_2$ requires C, 52·0; H, 3·5; Cl, 27·9%).

2-N-*Methylanilino*-4 : 6-*dihydroxypyrimidine*.—α-Phenyl-α-methylguanidine hydrochloride (8 g.) dissolved in ethanol (20 c.c.) was added to a solution of sodium (2 g.) in ethanol (40 c.c.), and, with the addition of ethyl malonate (6·3 g.), the mixture was heated under reflux on a steam-bath for 8 hours. After standing overnight, the precipitated sodium salt was collected and treated with dilute acetic acid. Crystallisation of the product from boiling water gave the *pyrimidine* (III, R = OH) (2·5 g.) as nearly colourless flat prisms, m. p. 219° (Found : C, 60·8; H, 4·9; N, 19·5. $C_{11}H_{11}O_2N_3$ requires C, 60·8; H, 5·0; N, 19·4%).

4 : 6-*Dichloro*-2-N-*methylanilinopyrimidine*.—(*a*) The colourless distillate obtained from the residue of the trichloropyrimidine preparation was crystallised from alcohol, and the *pyrimidine* (III, R = Cl) obtained in thick rhombic plates, m. p. 92—93° (Found : C, 52·0; H, 3·6; Cl, 27·6. $C_{11}H_9O_2Cl_2$ requires C, 52·0; H, 3·5; Cl, 27·9%).

(*b*) The dihydroxypyrimidine (III, R = OH) (2 g.) was heated under reflux with phosphoryl chloride (6 c.c.) for 15 minutes. The liquid was then poured on ice, and the precipitated solid collected and crystallised from ethanol (Found : C, 53·4; H, 3·8%). Admixture of the product with a specimen from the trichloropyrimidine preparation did not depress its m. p. of 92°.

4 : 6-*Dichloro*-5-p-*chlorobenzeneazo*-2-*methylpyrimidine*.—A mixture of 4 : 6-dihydroxy-5-*p*-chlorobenzeneazopyrimidine (5 g.), phosphoryl chloride (6 c.c.), and dimethylaniline (3 c.c.) was warmed until the solid dissolved. The black liquid was poured on ice, and after 1 hour the resinous product was separated by decantation and triturated with alcohol. Crystallisation of the orange solid (2·9 g.,

47%) from ethanol afforded the *azopyrimidine hemi-alcoholate* as clusters of bright red needles, m. p. 104° (Found : C, 44·7; H, 3·1. $C_{11}H_7N_4Cl_3,\frac{1}{2}EtOH$ requires C, 44·3; H, 3·1%).

2 : 4 : 6-*Trihydroxy*-5-p-*chlorobenzeneazopyrimidine* (cf. Lythgoe, Todd, and Topham, *loc. cit.*).—A cold aqueous solution of barbituric acid (15 g.) was treated with a solution of *p*-chlorobenzenediazonium chloride (from 15 g. of *p*-chloroaniline) in excess of concentrated hydrochloric acid. The solid which separated on basification with sodium hydrogen carbonate was collected, washed, and dried at 100°; the very sparingly soluble *azopyrimidine* crystallised from *cyclo*hexanone in minute yellow needles, m. p. 300° (Found : C, 45·0; H, 2·7. $C_{10}H_7O_3N_4Cl$ requires C, 44·9; H, 2·6%). The action of phosphoryl chloride–dimethylaniline on the azo-derivative gave an uncrystallisable resin.

DYSON PERRINS LABORATORY, OXFORD. [*Received, September 13th,* 1947.

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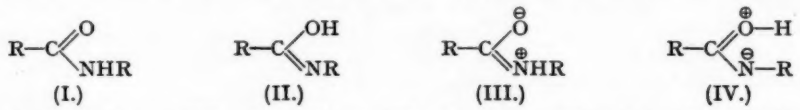
237. *Spectroscopic Studies of the Amide Linkage.*

By R. E. RICHARDS and H. W. THOMPSON.

The infra-red absorption spectra of a number of simple and substituted amides have been measured between 2 and 15 μ. The regions of particular interest are 5—7 μ and 3 μ, where absorption bands characteristic of the amide grouping occur. There are significant alterations in the spectra according to the state of aggregation in which the substance is measured, and these have an important bearing upon the interpretation of the results. A satisfactory explanation of the positions and shifts of the bands has been given. It is concluded that the amides exist predominantly in the ketonic form, which associates in the solid state through N–H···O bridges. The results provide a basis for more detailed studies on complex amides, amino-acids, and peptides.

THE correlation of the infra-red absorption spectra of simple molecules with the presence of particular structural groups has recently made it possible to apply the method successfully in studying polymers and macro-molecules. It is natural to enquire whether information can be obtained in this way about the structure of proteins, and other compounds in which the amide linkage forms an essential part. We have already obtained some promising results with nylon 66 and its derivatives, and new experimental methods suggest fresh possibilities for the infra-red examination of proteins. Other workers have also explored the subject (Wright, *J. Biol. Chem.*, 1939, **127**, 137; Buswell and Gore, *J. Physical Chem.*, 1942, **46**, 575). It remains certain, however, that before any detailed understanding of these more complicated molecules is achieved, much must first be explained about the spectra of simple amides and amino-acids.

The conventional plausible structures for an amide are the keto- (I; R = H) and the enol (II; R = H) form. Each of these structures would probably be stabilized by resonance with



(I.) (II.) (III.) (IV.)

a dipolar form, such as (III; R = H) or (IV; R = H). Hantzsch (*Ber.*, 1931, **64**, 661) measured the ultra-violet absorption spectra amides in various solvents, and concluded that in the cases studied—trichloroacetamide and benzamide—the enolic form predominates. On the other hand, more recent *X*-ray measurements by Senti and Harker (*J. Amer. Chem. Soc.*, 1940, **62**, 2008) show that in the solid state these molecules are associated into ring polymers, and that the occurrence of the enolic form is very unlikely. Some infra-red measurements by Buswell, Rodebush, and Roy (*ibid.*, 1938, **60**, 2444), by Buswell, Downing, and Rodebush (*ibid.*, 1940, **62**, 2759), and by Buswell and Gore (*J. Physical Chem.*, 1942, **46**, 575) have been described, but the results are not conclusive.

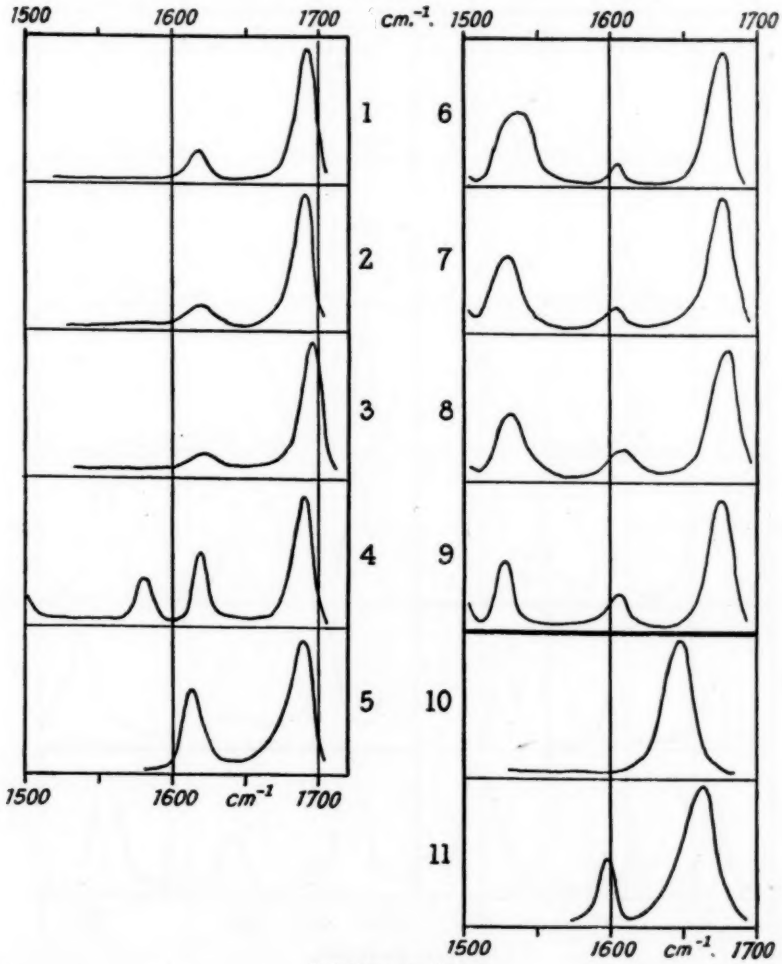
The amide grouping may be expected to have vibrational frequencies corresponding to the stretching of C:O, N–H, C:N, or O–H bonds, and also the associated bending oscillations. These several frequencies will be expected to give rise to absorption bands in the regions 5—7 μ and near 3 μ. Absorption bands due to less localized vibrations of the molecular skeleton as a whole will for the most part lie at wave-lengths longer than 7 μ, and between 7 and 14 μ at least are not usually very significant for our present purpose. Results are summarised below of measurements on the spectra of a number of amides in the solid state and in solution, and interpretations are suggested in terms of the possible molecular structure.

EXPERIMENTAL.

Between 7 and 15 μ the spectra were measured with a single-beam recording spectrometer using a rock-salt prism (Whiffen and Thompson, *J.*, 1945, 268). Most of the measurements considered here,

however, are for the regions 5—7 μ and 3 μ, for which a large double-beam recording spectrometer with calcium fluoride prism was used (Sutherland and Thompson, *Trans. Faraday Soc.*, 1945, **41**, 174; Thompson, Whiffen, Richards, and Temple, to be published shortly). This instrument not only has the marked advantage that there is no disturbance in the region 5—7 μ from the atmospheric water vapour band, but also use is made of the greater dispersion of fluorite compared with rock-salt. Calibration of wave-lengths was obtained with the absorption lines of water, ammonia, carbon dioxide (Oetjen, Kao, and Randall, *Rev. Sci. Instr.*, 1942, **13**, 515), nitrous oxide, and other substances. At about 1700 cm.$^{-1}$ the position of bands could be measured to within $\pm$ 3 cm.$^{-1}$, and at 3000 cm.$^{-1}$ to within $\pm$ 8 cm.$^{-1}$,

FIG. 1.



Solutions in dioxan.

1. *Butyramide.*
2. *Hexoamide.*
3. *Phenylacetamide.*
4. *Benzamide.*
5. *Furoamide.*
6. *Phenylacetomethylamide.*
7. *Phenylaceto*-tert.-*butylamide.*
8. *Phenylaceto*-tert.-*amylamide.*
9. *Phenylacetocyclohexylamide.*
10. *Acetodiethylamide.*
11. *Acetophenylmethylamide.*

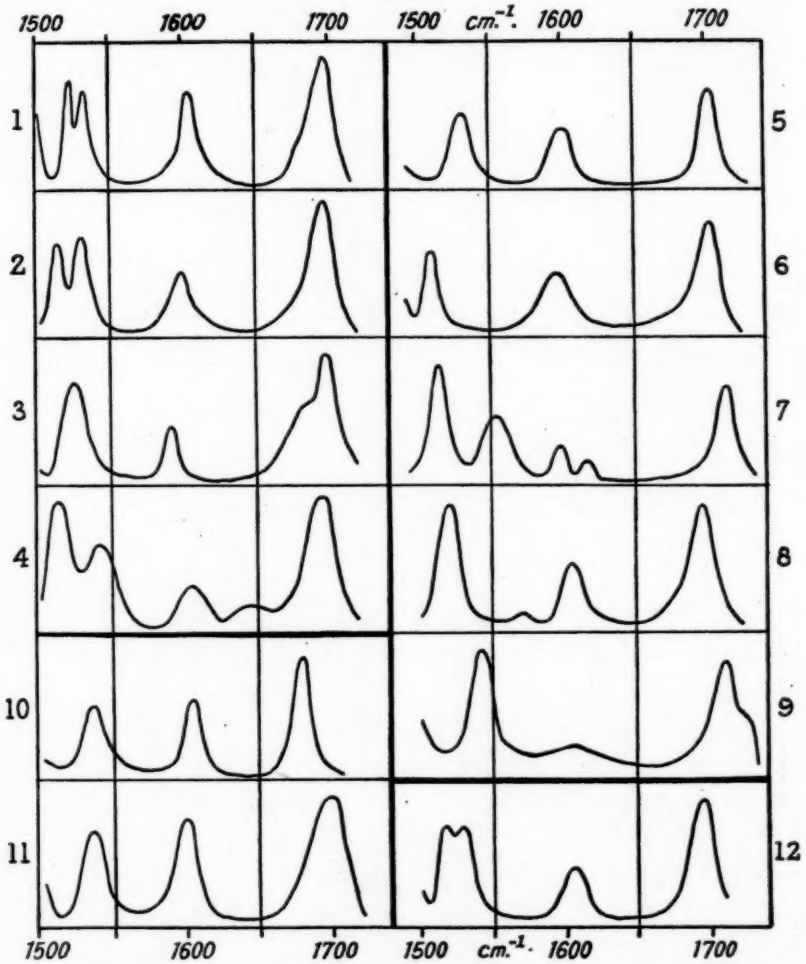
depending upon the breadth of the bands concerned. In many cases where comparisons were being made to discover a general trend, the relative positions of bands of different substances were probably more accurately determined than their absolute values, since several spectra could be measured on the same chart. As indication of the resolving power of the instrument, it was possible when using it as a single-beam spectrometer to resolve clearly lines 2—3 cm.$^{-1}$ apart at 1700 cm.$^{-1}$, and about 15 cm.$^{-1}$ apart at 3000 cm.$^{-1}$; with the double-beam arrangement, which necessitated somewhat wider slits, the corresponding figures were about 5 cm.$^{-1}$ and 20 cm.$^{-1}$.

Solutions were measured in cells 0·01 and 0·2 cm. in thickness, according to the dilution used. The choice of solvent is limited by the solubilities of these compounds, and by the absorption of the solvent.

Dioxan, chloroform, methyl cyanide, and methanol were normally used, being purified in the standard manner. Amides were measured in the solid state by grinding to a fine paste with medicinal paraffin and pressing between a pair of rock-salt plates. By suitable adjustment of the size of the particles, specimens prepared in this way produce little scattering and a satisfactory spectrum can be obtained with only a few mg. of the solid.

The compounds examined were either prepared in this laboratory or obtained commercially. In all cases they were purified by recrystallisation or other appropriate methods.

FIG. 2.



Solutions in dioxan.

1. *Acetanilide.*
2. *Aceto*-p-*toluidide.*
3. *Aceto*-o-*toluidide.*
4. *Aceto*-p-*methoxyanilide.*
5. p-*Chloroacetanilide.*
6. p-*Bromoacetanilide.*
7. p-*Nitroacetanilide.*
8. 3-*Bromoaceto*-p-*toluidide.*
9. 3-*Bromo*-5-*nitroaceto*-p-*toluidide.*
10. *Benzanilide.*
11. *Phenylacetanilide.*
12. *Phenylaceto*-p-*toluidide.*

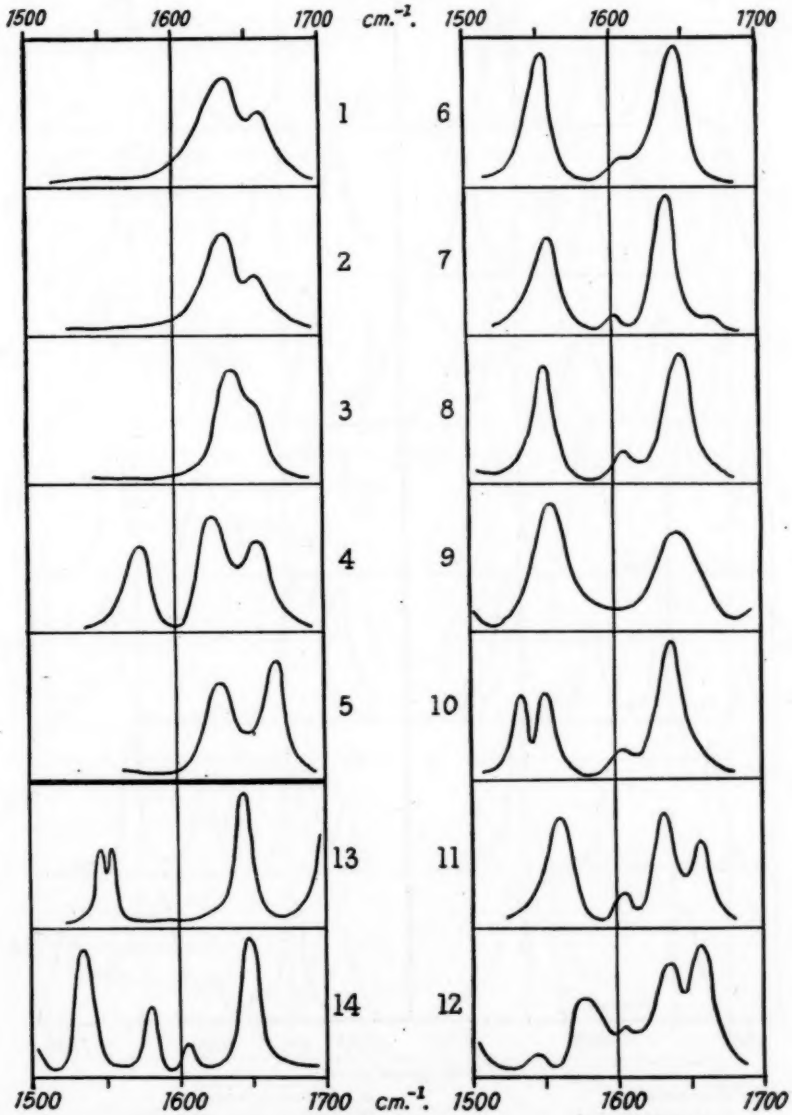
Results.—Solutions in dioxan. Fig. 1 shows the spectra (1—5) of five simple unsubstituted amides in dioxan near 6 μ. Any effect of this solvent on C=O or C=N groups by association or similar interactions must be negligibly small. Two bands occur in this region, a strong one near 1690 cm.$^{-1}$ and a weaker one of somewhat variable intensity at 1615—1620 cm.$^{-1}$. Fig. 1 also shows (6—9) some *N*-alkyl monosubstituted amides, which exhibit two bands at 1675—1680 cm.$^{-1}$ and 1530—1540 cm.$^{-1}$. In these cases the latter band is more marked in intensity than the band of the unsubstituted amides at 1615—1620. With the two *NN*-disubstituted amides there is only one band, near 1650 cm.$^{-1}$ unless a phenyl group is one of the substituents, in which case the band lies at slightly higher frequencies. All the compounds containing a phenyl group show the well-known sharp, even if weak, bands near 1500 and 1600 cm.$^{-1}$. These results are summarised broadly in Table I. The band at the higher frequencies will be called the A band, and that at the lower frequency the B band.

TABLE I.

Solutions in dioxan.

	Band A.	Band B.
$R{\cdot}CO{\cdot}NH_2$	1690	1620
$R{\cdot}CO{\cdot}NHAlk$	1680	1530
$R{\cdot}CO{\cdot}NR_1R_2$	1650	—

FIG. 3.



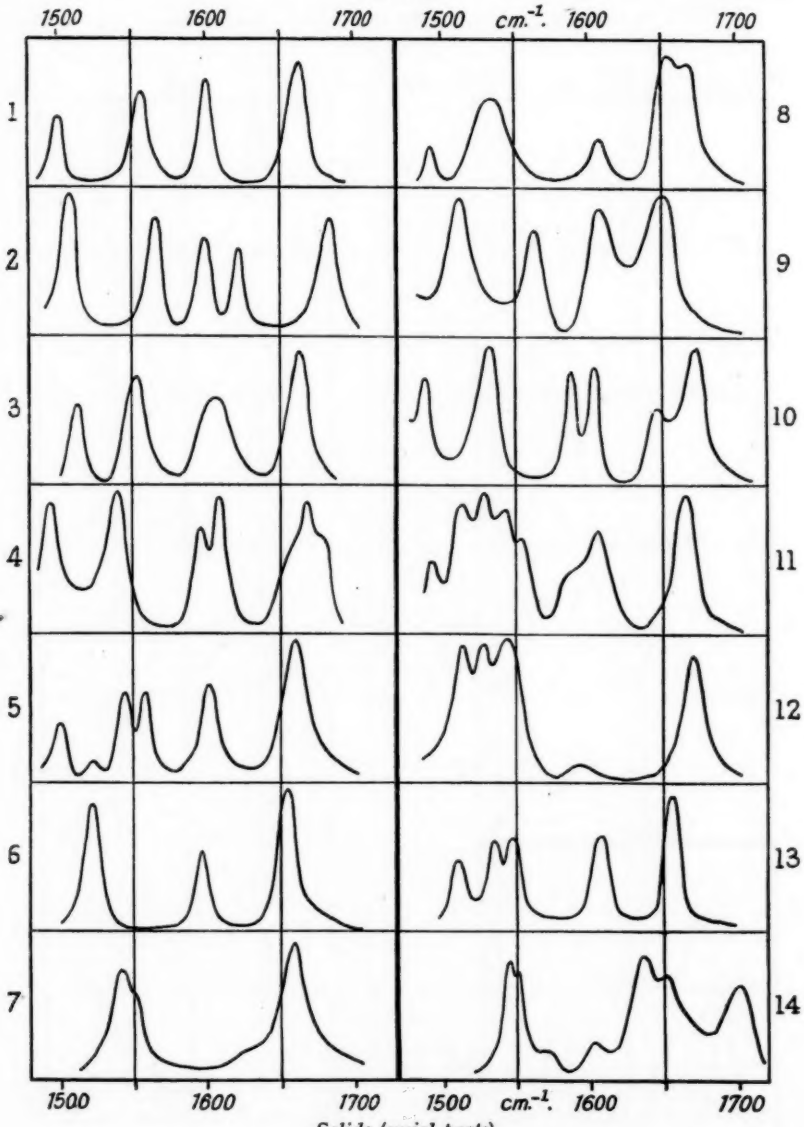
Solids (nujol paste).

1. *Butyramide.*
2. *Hexoamide.*
3. *Phenylacetamide.*
4. *Benzamide.*
5. *Furoamide.*
6. *Phenylaceto*-tert.-*amylamide.*
7. *Phenylaceto*cyclo*hexylamide.*
8. *Phenylaceto*-tert.-*butylamide.*
9. *Methyl phenylacetamidoacetate.*
10. *Phenylacetobenzylamide.*
11. *Phenylaceto*-n-*propylamide.*
12. *Phenylacetomethylamide.*
13. N-*Hexoylglycine.*
14. *Ethyl hippurate.*

The results suggest that the band B only appears when there is at least one hydrogen atom in the amide group, and that both the bands A and B are lowered in frequency by substitution of alkyl groups on the nitrogen atom.

Fig. 2 shows the spectra of some derivatives of acetanilide in dioxan. The main feature with these compounds is that the band A lies at about 1700 cm.$^{-1}$, distinctly higher than with the *N*-alkyl-substituted amides. It should be noted that when the group attached to the nitrogen atom is strongly electrophilic, the frequency of this band is further raised, and although such increases of 10—15 cm.$^{-1}$

FIG. 4.



Solids (nujol paste).

1. *Acetanilide.*
2. p-*Nitroacetanilide.*
3. *Aceto*-p-*toluidide.*
4. p-*Chloroacetanilide.*
5. *Phenylacetanilide.*
6. *Phenylaceto*-o-*toluidide.*
7. *Phenylacetamidomethyl cyanide.*
8. *Aceto*-o-*toluidide.*
9. *Aceto*-p-*methoxyanilide.*
10. p-*Bromoacetanilide.*
11. 3-*Bromoaceto*-p-*toluidide.*
12. 3-*Bromo*-5-*nitroaceto*-p-*toluidide.*
13. *Phenylaceto*-p-*toluidide.*
14. *Hippuramide.*

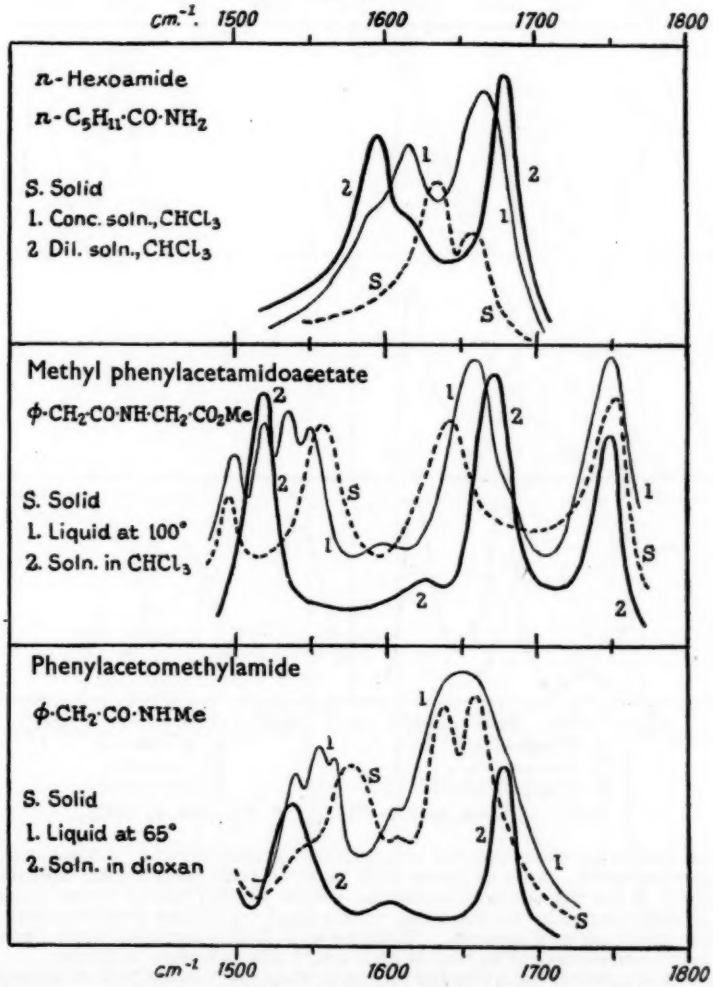
may be regarded as small, they are nevertheless real and regular. Conversely, we should expect electrophobic substituents to lower the frequency, and this seems to occur. As regards the band B of the acetanilides, although there is some interference in the region 1500—1550 cm.$^{-1}$ from bands due to the aromatic ring and other substituent groupings, there seems to be a less definite influence of the *N*-substituents upon its position.

Solutions in other solvents. Many of the amides have also been measured in chloroform and methanol, with particular reference to the position of the band A. The general behaviour found with all amides is that the frequency of this band falls in passing along the series dioxan, chloroform, methanol, and is illustrated by the examples listed in Table II.

TABLE II.

	Frequency (cm.$^{-1}$) of band A in :		
	Dioxan.	Chloroform.	Methanol.
Hexoamide	1692	1682	1672
Phenylaceto-*tert.*-amylamide	1682	1668	1657
Aceto-*NN*-diethylamide	1647	1629	1615 (broad)

FIG. 5.



(1) *Hexoamide* : s. *Solid.* 1. *Conc. soln. in* $CHCl_3$. 2. *Dil. soln. in* $CHCl_3$.
(2) *Methyl phenylacetamidoacetate* : s. *Solid.* 1. *Liquid at* 100°. 2. *Solution in* $CHCl_3$.
(3) *Phenylacetomethylamide* : s. *Solid.* 1. *Liquid at* 65°. 2. *Solution in dioxan.*

Solids. The spectra of a number of solid amides measured as a paste in " Nujol " in the region of 6 μ are shown in Fig. 3. In Fig. 4, further examples are given of *N*-monosubstituted amides in which the substituent group has either electron-attracting or electron-repelling character. The simple unsubstituted amides show two fairly close bands in the region 1620—1670 cm.$^{-1}$. The *N*-alkylamides show bands at about 1560 and 1640 cm.$^{-1}$, whereas the amides with electrophilic *N*-substituents have the second band—the band A mentioned above—at higher frequencies than 1640 cm.$^{-1}$. The position of the band B is variable, as found with the solutions in dioxan. One solid *NN*-disubstituted amide, namely aceto-*N*-methylanilide, was examined and the position of the band A was hardly affected in

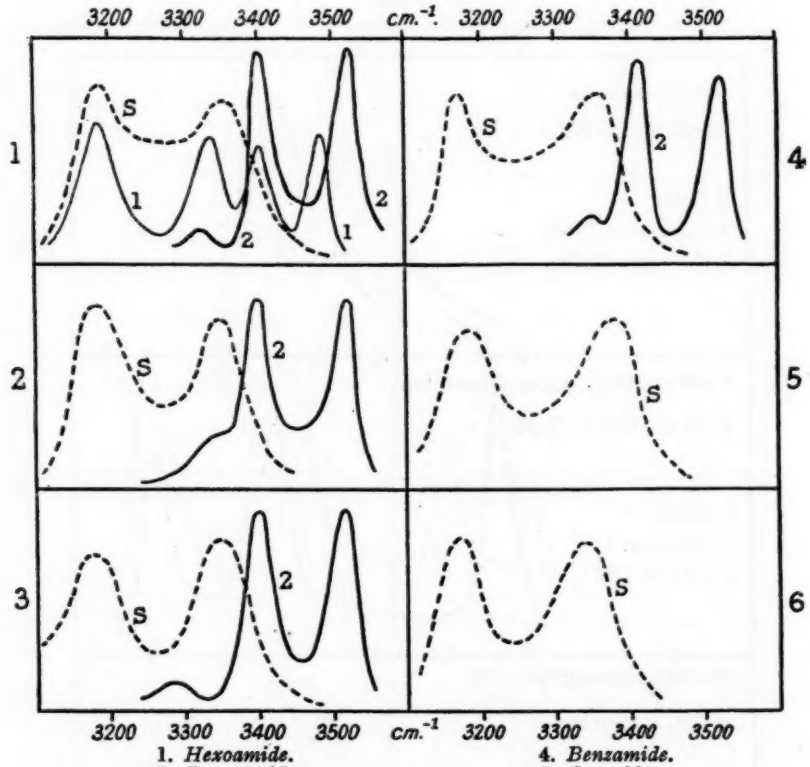
passing from solution in dioxan to the solid state. The above results are summarised broadly in Table III.

TABLE III.

Solids (R = alkyl, R_e = electrophilic group).

	Approximate position ($cm.^{-1}$) of bands: A.	B.
$R'\cdot CO\cdot NH_2$	1655	1630
$R'\cdot CO\cdot NHR$	1640	1560
$R'\cdot CO\cdot NHR_e$	1660—1680	1530—1570

FIG. 6.



1. *Hexoamide.* 4. *Benzamide.*
2. *Butyramide.* 5. *Oxamide.*
3. *Phenylacetamide.* 6. *Succinamide.*

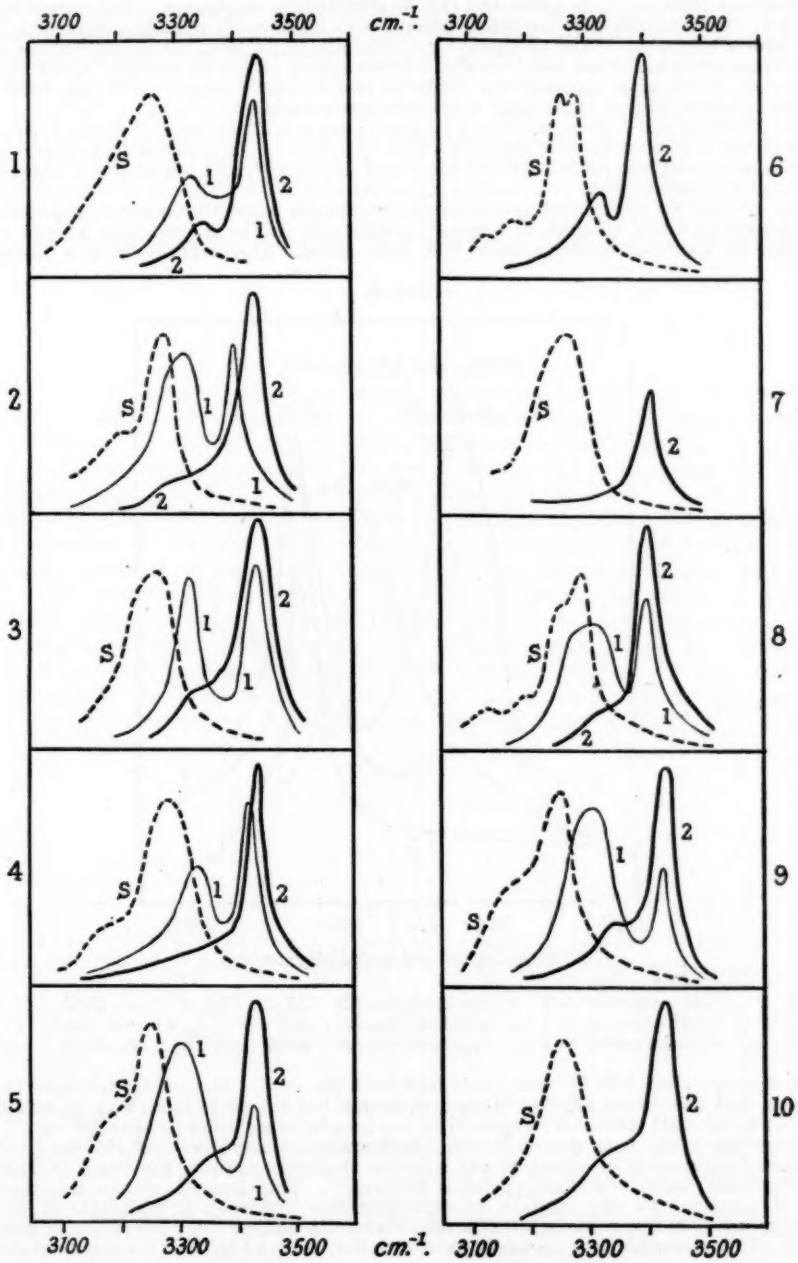
s. *Solid.* 1. *Conc. soln. in* $CHCl_3$. 2. *Dil. soln. in* $CHCl_3$.

It can be seen that in the solid state the unsubstituted amides show the A band at about 1655 $cm.^{-1}$, and the *N*-alkyl-substituted amides at about 1640 $cm.^{-1}$, in both cases a noticeable decrease from the values found (Table I) for the solutions in dioxan. With the *NN*-disubstituted amides, either liquid or solid, there is little change in the frequency of this band on passing from the liquid or solid to the solution, although the band may broaden. With the solid *N*-alkylamides a fairly strong band appears at about 1560 $cm.^{-1}$, corresponding to that at 1530 $cm.^{-1}$ with solutions in dioxan.

The increase in frequency of the A band of the solids when the *N*-substituent is electrophilic is parallel to the change found with the solutions. It may also be noted that when this band is raised in frequency by the electrophilic substituent, the band normally at 1560 $cm.^{-1}$ is generally lowered. Finally, the relative intensity of the bands A and B appears to alter with the change of state, the latter usually becoming stronger with the solid.

Gradual Transitions from Solid or Liquid to Dilute Solution.—Several examples have been examined of the changes associated with the transition from the solid or liquid amide to a very dilute solution, through intermediate concentrations of the solute. Some of the results are shown in Fig. 5 for *n*-hexoamide, phenylacetomethylamide, and methyl phenylacetamidoacetate in chloroform. Some of bands shown are connected with groups with which we are not immediately concerned; for example, that at 1750 $cm.^{-1}$ due to the carbonyl group of the ester. The main point to notice is that in every case the passage from the solid (or liquid) to the dilute solution brings about an increase in the frequency of the band A and a simultaneous decrease in the frequency of the band B. Thus with hexoamide, the

FIG. 7.



1. *Phenylacetomethylamide.*
2. *Phenylaceto*-tert.-*butylamide.*
3. *Phenylaceto*-n-*propylamide.*
4. *Phenylaceto*-tert.-*amylamide.*
5. *Phenylacetocyclohexylamide.*
6. *Phenylacetanilide.*
7. *Phenylaceto*-o-*toluidide.*
8. *Phenylaceto*-p-*toluidide.*
9. *Phenylacetamidomethyl cyanide.*
10. *Methyl phenylacetamidoacetate.*

s. *Solid.* 1. *Conc. soln. in* $CHCl_3$. 2. *Dil. soln. in* $CHCl_3$.

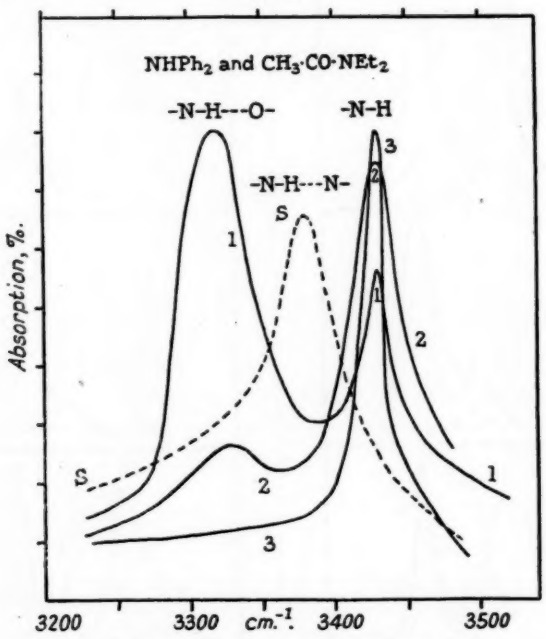
solid has the bands at 1655 and 1635 cm.$^{-1}$, in concentrated solution they lie at 1668 and 1615 cm.$^{-1}$, and in dilute solution at 1680 and 1595 cm.$^{-1}$. With methyl phenylacetamidoacetate the solid has bands at 1642 and 1557 cm.$^{-1}$, the liquid (at 100°) at 1660 and 1535 cm.$^{-1}$, and the solution in chloroform at 1672 and 1517 cm.$^{-1}$. (The band at about 1750 is due to the carbonyl link in the ester group.)

The region of 3 μ. The spectra of many unsubstituted and *N*-substituted amides have been measured between 3000 and 3600 cm.$^{-1}$, as solids and also as solutions in chloroform. The curves are shown in Figs. 6 and 7. With substances containing phenyl radicals, there is usually a band near 3070 cm.$^{-1}$ connected with a vibration of the aromatic C–H linkages, but this is not significant for our present purpose. Dilute solutions of the unsubstituted amides appear to have two sharp bands at about 3400 and 3520 cm.$^{-1}$, which give place in the solids to two others at about 3180 and 3350 cm.$^{-1}$. In concentrated solutions all four bands may appear simultaneously.

In dilute solutions, the *N*-monosubstituted amides have one sharp band at about 3430 cm.$^{-1}$ which gives place in the solid to a broader band at about 3270 cm.$^{-1}$. In concentrated solutions the latter band seems to appear at frequencies rather higher than 3270 cm.$^{-1}$, and can be found concurrently with the sharp band near 3430 cm.$^{-1}$.

In connexion with the possible interpretation of these bands and shifts, we have examined the spectra of diphenylamine in dilute solution in carbon tetrachloride and as a solid, and also of solutions of diphenylamine to which acetodiethylamide had been added. This experiment is a variant on that

FIG. 8.



Diphenylamine and acetodiethylamide.

s. *Solid diphenylamine.*
1. 2 *G. diphenylamine* + 1 *c.c. acetodiethylamide* : 25 *c.c.* CCl_4, 0·1 *mm. thick.*
2. 2 *G. diphenylamine* + 1 *c.c. acetodiethylamide* : 500 *c.c.* CCl_4, 2·0 *mm. thick.*
3. 2 *G. diphenylamine* + 1 *c.c. acetodiethylamide* : 5000 *c.c.* CCl_4, 2 *cm. thick.*

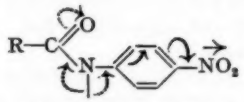
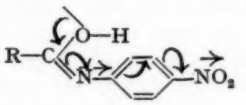
previously described by Buswell, Downing, and Rodebush (*loc. cit.*). The results are depicted in Fig. 8. It can be seen that the dilute solution of diphenylamine has the N–H stretching vibration band at 3430 cm.$^{-1}$, but in the solid state this is replaced by the broader association band at 3380 cm.$^{-1}$. Similar N–H---N association has been recorded with ethyleneimine (Thompson and Harris, *J.*, 1944, 301). When the acetodiethylamide is added to the solution of diphenylamine, the band at 3430 cm.$^{-1}$ is diminished in intensity and a new band appears at 3320 cm.$^{-1}$. This change corresponds to the formation of N–H---O bridges. As the mixture of diphenylamine and acetodiethylamide is diluted, the association band at 3320 cm.$^{-1}$ is much diminished whilst the normal N–H frequency at 3430 cm.$^{-1}$ is strengthened. This phenomenon is markedly parallel to that seen in Fig. 7 for the *N*-substituted amides.

DISCUSSION.

The results described above show that the vibration frequencies exhibited by amides are much affected by the change of state from solid to solution. It will be convenient first to consider the spectra of solutions before discussing the shifts which occur on passing to the solids.

As already stated, a simple *N*-monosubstituted amide could exist as either the ketonic (I) or the enolic (II) form, each of these being capable of hybridisation with its corresponding dipolar structure, (III) and (IV), respectively. The band A of *NN*-disubstituted amides which occurs at about 1650 cm.$^{-1}$ must be attributed to the stretching vibration of the C=O bond, since

no enolisation of the conventional type can occur. The lower value as compared with that in ketones—about 1710 cm.$^{-1}$—will result from the resonance with the ionic form. In the case of the simple or *N*-monosubstituted amides the band A could be interpreted in the same way. In this case, however, enolisation would lead to some form of C=N link, and it is well known from the Raman spectra of ketoximes that this can give rise to a band in the region 1650—1660 cm.$^{-1}$ (Hibben, " The Raman Effect," p. 280). Now the above measurements with the amides having a strongly electrophilic *N*-substituent provide an argument against this correlation of the band A with the vibration of a C=N bond, as follows. If the amide has the ketonic form, the presence of strongly electrophilic groups on the nitrogen atom should cause the dipolar form (III) to be less stable relative to the non-polar form (I). Alternatively, the electron-attracting groups can be regarded as opposing the conjugation from the nitrogen atom to the carbonyl group, as in

(V.)   (VI.)

(V). In these circumstances the carbonyl group will be expected to have greater double-bond character, and a rather higher stretching-vibration frequency, which is in fact found. If the molecule existed in the enolic form, however, the converse would apply. An electrophilic substituent on the nitrogen atom would then favour the dipolar form, shown by (VI), and the double-bond character of the C=N bond would be lowered.

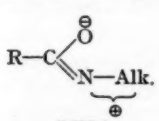
It therefore seems satisfactory to attribute the band A in the amides as a whole to the stretching vibration of the essentially ketonic carbonyl group. In connexion with these arguments it is interesting to consider the effect of *N*-alkyl substituents upon the frequency of the band A. The results of Table I and Fig. 1 suggest that these groups have an opposite effect to those groups which are known to be electron-attracting. Now, alkyl groups are known to be readily polarisable (Ingold, *Chem. Reviews*, 1934, **15**, 238), that is, they can provide or accept electrons according to the particular group to which they are attached. This is well illustrated by the values for the dipole moments of some simple compounds quoted by Watson (" Modern Theories of Organic Chemistry," 2nd edition, p. 93), and listed in Table IV. It is possible,

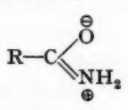
TABLE IV.

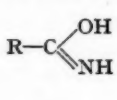
Dipole moments of compounds RX.

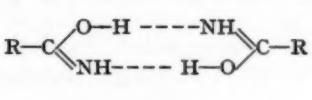
R/X =	Cl.	Br.	I.	CN.	NO_2.	OH.
H	1·03	0·78	0·38	2·93	—	1·84
CH_3	1·87	1·80	1·64	3·94	3·54	1·69
C_2H_5	2·05	2·01	1·87	4·04	3·58	1·69

therefore, that in the alkyl-substituted amides the fractional positive charge on the nitrogen atom is shared by the alkyl group. In other words, the energy of the charge separation in (VII)

 (VII.)

 (VIII.)

 (IX.)

 (X.)

is lower than in (VIII). In that case, the relative contribution of (VII) to the hybrid will be greater than that of (VIII), so that the carbonyl group will have less double-bond character and a lower vibration frequency in the alkyl derivatives.

The interpretation of the band B found between 1520 and 1630 cm.$^{-1}$ with the unsubstituted and *N*-monosubstituted amides is more difficult. It might be explained in four ways, namely, (i) as the stretching vibration of the C–N link in a ketonic form, if this bond has acquired considerable double-bond character due to resonance with the dipolar form; (ii) as the stretching vibration of the C=N link in an enolic form, reduced in frequency by resonance with its dipolar structure; (iii) as a bending frequency of the N–H link; or (iv) as an overtone or combination band. As already explained, the band is not observed with disubstituted amides where there will certainly be contributions from the dipolar form. Also, the degree of double-bond character required to produce such a high frequency seems much greater than is plausible from the molecular bond lengths found in some solid amides such as acetamide (Senti and Harker, *loc. cit.*). These arguments make the first interpretation improbable.

The assignment of the band B to the C=N link of an enolic form would imply the simultaneous existence of both ketonic and enolic forms both in solution and in the solid state. The *X*-ray measurements have shown, however, that in the solid state only the ketonic form is present. Further, in no case is the shift produced by the substitution of an electron-attracting group by an alkyl group consistent with this interpretation. Also, the band B increases in frequency on passing from the solution to the solid. This is contrary to what would be expected if this change were accompanied by the formation of bridged links in passing from (IX) to (X).

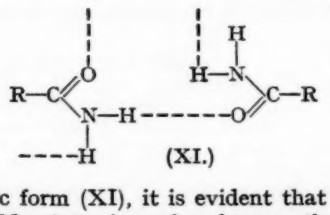
Finally, if an amide were to exist as a mixture of the ketonic and the enolic form, samples from different sources and recrystallised from different solvents would be expected to show different proportions of the two forms. In no case have such variations been detected.

The possibility that the band B is due to an overtone cannot be ruled out, but it is improbable. The band varies in intensity in different compounds, but with the *N*-monosubstituted derivatives it is usually stronger than might be expected for anything but a fundamental. Experiments with deuterated compounds might help to settle this question.

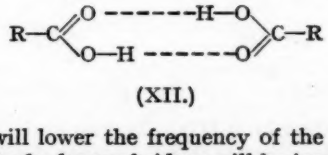
The third possibility seems to us the most reasonable. It explains the absence of the band in the disubstituted amides, and the shift of the band B in passing from the solid to solution—namely, a decrease in frequency—agrees with that expected of a bending mode of the N–H link if the latter takes part in hydrogen bridges in the solid state. The difference between the band B in unsubstituted amides on the one hand, and *N*-monosubstituted amides on the other, can be explained by interaction between the two N–H bonds in the former case. Hence, it seems that in dilute solution in dioxan, the amides exist predominantly in the ketonic form.

The results of Table II illustrate the effect of solvent on the stretching frequency of the carbonyl group. This may be due to two causes, namely, the difference in dielectric constant of the medium, or the effect of hydrogen bonding from the solvent to the carbonyl group of the amide. The energy of the charge separation in (VII) or (VIII) might be lowered by an increase in the dielectric constant of the medium, and the stretching frequency of the carbonyl group would then be expected to lie at lower values than in a medium of low dielectric constant. In methyl cyanide, however ($\varepsilon = 37{\cdot}5$), the frequency of the carbonyl group is substantially the same as in dioxan ($\varepsilon = 2{\cdot}2$), so this influence of dielectric constant cannot be very significant. On the other hand, solvation by hydrogen bonding to a carbonyl group lowers the frequency of the latter. With acetone in carbon tetrachloride solution, it lies at 1710 cm.$^{-1}$, but in methyl alcohol at 1701 cm.$^{-1}$. It is therefore possible that the changes shown in Table II are caused by a change in hydrogen bonding from the solvent to the carbonyl group.

In the solid state, the stretching frequency of the carbonyl group in an unsubstituted or *N*-monosubstituted amide lies at a much lower value than in dilute solution in dioxan, whilst the band B lies at higher values. Our own measurements, and those of Gordy (*J. Chem. Physics*, **1939, 7**, 163) show, as just outlined, that the frequency of the carbonyl group is reduced by hydrogen bonding. Since the *X*-ray measurements indicate that acetamide exists in a



(XI.)



(XII.)

polymeric form (XI), it is evident that the bonding will lower the frequency of the carbonyl group. Moreover, in such polymers, the strength of the hydrogen bridges will be increased by the presence of a greater positive charge on the nitrogen atom, or a greater negative charge on the oxygen atom, and therefore by an increase in the contribution of the dipolar structure to the hybrid. It follows that in the associated form of the amides the carbonyl link will have a smaller double-bond character than in the unassociated form, and hence a lower frequency of vibration. The *NN*-disubstituted amides, which cannot undergo such association, show no such shifts of the frequency with change of state.

That this association has a powerful effect on the stretching vibration frequency of the carbonyl group is further borne out by our measurements on acetic acid and phenylacetic acid in the liquid and in the solid state, where the substances are known to exist as dimers of the type (XII). With liquid acetic acid the band lies at 1712 cm.$^{-1}$, and with solid phenylacetic acid there is a double band at 1704—1692 cm.$^{-1}$. A dilute solution of acetic acid in dioxan, however, shows bands at 1730 and 1753 cm.$^{-1}$, which may correspond to the dimeric and the monomeric

form. Herman and Hofstadter (*J. Chem. Physics*, 1939, **7**, 460) have similarly shown that in the vapour state the frequencies of the carbonyl group in dimeric and monomeric aliphatic acids lie at about 1740 and 1770 cm.$^{-1}$, so the shift is about 30 cm.$^{-1}$. In dioxan, phenylacetic acid shows one sharp band at 1735 cm.$^{-1}$, and the shift in passing from the dimer to the monomer is therefore closely parallel to that found with amides in passing from solutions in dioxan to the solid state.

If this interpretation of the shift is correct, we might expect that in concentrated solutions of the amides, the co-existence of both unassociated and associated forms might give rise to two frequencies of the carbonyl group, and there is some evidence to support this. The curves of Fig. 5 show that the band due to the carbonyl group is broad with concentrated solutions of hexoamide and phenylaceto-*tert.*-butylamide, and there are signs of a double band. Dilute solutions of hexoamide in chloroform show three bands at 1595 (strong), 1615 (weak), and 1678 (strong and sharp), whereas with concentrated solutions the bands are at 1595 (weak), 1615 (strong), and 1668 (strong and broad). This suggests that in concentrated solutions the dimers giving rise to 1615, 1668 predominate, whilst in dilute solutions the monomer (1595, 1678) is in excess. Two amides were examined as liquids at temperatures above their melting point, and the bands A and B were displaced to positions intermediate between those found for the solids and for the solutions, and were also broad suggesting the presence of more than one species.

To sum up, therefore, the bands in the region 5—7 μ suggest that amides have the ketonic structure, resonating with its corresponding dipolar form. In dilute solution in dioxan and chloroform the amides appear to be monomeric, but in more concentrated solutions in chloroform, and in the liquid state, association occurs. In the solid state this association is complete.

In the region of 3 μ we should expect to find absorption bands due to the stretching vibration of N–H links, and of O–H links if present. In dilute solutions, the unsubstituted amides show sharp bands at about 3400 cm.$^{-1}$ and 3520 cm.$^{-1}$, which might at once be correlated with the symmetrical and antisymmetrical vibrations of the NH_2 group in an unassociated form. On the other hand, the band at 3520 cm.$^{-1}$ might be assigned to the O–H link of an enolic form. However, the frequency due to the unassociated hydroxyl link in a large number of alcohols and phenols lies between 3610 and 3680 cm.$^{-1}$, and with fatty acids at about 3550 cm.$^{-1}$. We might therefore expect the unassociated hydroxyl band in an enolized amide to lie at about 3600 cm.$^{-1}$. Only in the case of trichloroacetic acid (Buswell, Rodebush, and Roy, *J. Amer. Chem. Soc.*, 1938, **60**, 2239) does this band lie at a frequency as low as 3520 cm.$^{-1}$, and in this case the O–H link must certainly be weaker than in the amide. Hence it is unlikely that the amide band at 3520 cm.$^{-1}$ could be due to the hydroxyl group, and the explanation given at the start is to be preferred.

In very dilute solution, the *N*-monosubstituted amides show one band at 3420—3440 cm.$^{-1}$. This low value cannot possibly be due to an enolic O–H group, and lies as expected between the two frequencies of the unsubstituted amides. *NN*-Disubstituted amides show no absorption in this region.

In the solid state, the unsubstituted amides have strong bands at about 3180 and 3350 cm.$^{-1}$, which are plausibly interpreted as being due to two bonded N–H groups of a polymeric complex such as was indicated above. In the concentrated solutions, illustrated for hexoamide in Fig. 6, both the association bands at 3180, 3350 cm.$^{-1}$, and the unassociated N–H bands at 3400, 3520 cm.$^{-1}$ appear simultaneously.

N-Monosubstituted amides have one band only in the solid state, at 3270 cm.$^{-1}$, which again corresponds to a bonded N–H group. Here too, in concentrated solutions, both the association band and the " normal " band at 3430 cm.$^{-1}$ are simultaneously present. In these cases the association band appears to shift gradually towards higher frequencies and has a diminishing intensity as the dilution is increased, which would imply some gradual weakening of the bonding strength.

This interpretation of the bands of *N*-monosubstituted amides near 3 μ is supported by the measurements already described with diphenylamine and acetodiethylamide. These showed that the unbonded N–H link in diphenylamine has a frequency of 3430 cm.$^{-1}$, and the strongly bonded N–H – – –O group has a frequency of 3320 cm.$^{-1}$. These values fall exactly into line with those for the unsubstituted amides.

It seems, therefore, that the spectroscopic data in both the regions, 3 μ and 6 μ, indicate the existence of the amides in the ketonic form, which associates through N–H – – –O bonds in concentrated solutions, in the liquids and in the solids. This preliminary survey will be useful in our later consideration of the more complex amides, amino-acids, and peptides.

We thank the Government Grant Committee of the Royal Society for a grant in aid of equipment, and the Department of Scientific and Industrial Research for a Maintenance Grant to one of us. We are also pleased to record appreciation of some valuable discussions which one of us had with workers at the University of Michigan, and at the Shell Development Company, Emeryville, during 1945, on the above and related problems.

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[*Received, November 6th*, 1946.]

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238. *Vibrational Spectra of Phenolic Derivatives and Phenolic Resins.*

By R. E. RICHARDS and H. W. THOMPSON.

The vibrational spectra of some substituted phenols and related compounds, and of some resins formed from phenols and aldehydes, have been examined. The possibility of formulating correlation rules for use in determining structural features of the resins has been explored. From the bands observed in the region 700—900 cm.$^{-1}$ it may be possible to infer the type of substitution around the aromatic nuclei in these complex molecules. The absorption of hydroxyl groups in the region 3200—3650 cm.$^{-1}$ reveals differences in the types of hydrogen bonds in the different compounds and suggests that differences between resins made from the same materials may be related to this particular structural feature. Some of the compounds have been measured both as solids and as liquids and spectral differences in the two states of aggregation have been found.

INFRA-RED spectroscopy has recently been used in examining compounds of high molecular weight, and some results have emerged which might not have been derivable by other methods (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 246; *Proc. Roy. Soc.*, 1945, **184**, *A*, 3, 21). Among other classes of compound we have studied the resins formed by condensation of phenols with aldehydes, the aim being to discover more about the mechanism of condensation and the nature of cross linkage in these structures. Whilst some empirical spectral differences between different resins were of immediate practical interest, it became clear that the only satisfactory way of understanding the spectra would be to collect results for a large number of structurally related simpler molecules from which closer correlations with molecular structure could be made. In the course of this investigation some interesting facts have emerged about the association which occurs with these hydroxylic compounds, and the nature of the hydrogen bridges which arise. Some of the results are given in the present paper.

EXPERIMENTAL.

The spectra between 6 and 15 μ were measured on a single-beam recording spectrometer with rock-salt prism (Whiffen and Thompson, *J.*, 1945, 268). The measured frequencies were accurate to ± 5 cm.$^{-1}$ at 7 μ, and to ± 2 cm.$^{-1}$ at 15 μ. Between 2·5 and 6 μ a double-beam recording spectrometer was used (see preceding paper). With this spectrometer, the frequencies of bands near 7 μ could be determined to ± 3 cm.$^{-1}$, and at 3 μ to ± 8 cm.$^{-1}$ depending upon their breadth. At 3 μ it was possible to resolve bands 20 cm.$^{-1}$ apart, although when the instrument was used as a single-beam spectrometer rather better resolution was possible.

Solutions in carbon disulphide were measured in rock-salt cells about 0·1 mm. thick. Solutions in carbon tetrachloride were studied at 3 μ in rock-salt cells of thickness 2 mm., 3·5 cm., and 7·8 cm., according to the dilution being used. Solids were examined either by melting them and allowing them to crystallise between a pair of rock-salt plates, or by the method of a paste in paraffin used in the preceding paper. Measurements at higher temperatures were made with an electrically heated cell (Richards and Thompson, *Trans. Faraday Soc.*, 1945, **41**, 183).

Many of the phenolic derivatives were kindly supplied by Messrs. Bakelite Ltd. or by the Chemical Laboratory, Teddington. Others were commercial samples purified in this laboratory in the appropriate manner. The resins were supplied by Messrs. Bakelite Ltd. and by other firms.

RESULTS AND DISCUSSION.

Figs. 1 and 2 show the spectra between 700 and 1500 cm.$^{-1}$ (14—6·5 μ) of some phenols, aromatic alcohols, and other compounds likely to have a bearing on the structure of the resins themselves. Each of the spectra is complex, and few correlations are immediately obvious. All the compounds show one or more intense bands in the region 700—870 cm.$^{-1}$, and these are of particular interest since it has previously been found that substituted benzenes have more or less characteristic frequencies in this range, according to the number and position of the substituents and in great measure independent of their exact nature (Thompson and Torkington, *loc. cit.*; Whiffen and Thompson, *loc. cit.*). The normal vibration of benzene in which the group of six carbon atoms moves in a rigid plane perpendicularly to the plane containing the six

hydrogen atoms has a frequency of 671 cm.$^{-1}$. Previous results have shown that when the substituent is attached to the ring, this type of vibration, which is essentially a deformation of the remaining C–H bonds, is displaced to 740—760 cm.$^{-1}$. With disubstituted benzenes, the corresponding vibration has a frequency which depends on the relative position of the substituents; with *o*-derivatives it usually lies at 740—760 cm.$^{-1}$, with *m*-compounds at 770—790 cm.$^{-1}$, and with *p*-compounds at 810—830 cm.$^{-1}$. With tri- and tetra-substituted benzenes the corresponding deformations of the residual C–H bonds also appear to have fairly definite frequencies. The earlier work suggested for the 1 : 2 : 3-derivatives a band at 760—770 cm.$^{-1}$, for 1 : 2 : 4-compounds a band at 800—820 cm.$^{-1}$, and for 1 : 3 : 5-compounds at 825—860 cm.$^{-1}$. With the 1 : 2 : 3 : 5- or 1 : 2 : 4 : 5-compounds the band lies in the region 850—880 cm.$^{-1}$.

The present results appear in most cases to conform with these correlations. Thus, mono-substituted benzenes include:

Benzyl alcohol	745 cm.$^{-1}$	Diphenyl ether	752 cm.$^{-1}$
β-Phenylethyl alcohol	748 ,,	Diphenylmethane	735 ,,
Dibenzyl ether	746 ,,		

Typical disubstituted benzenes include the following:

ortho-.		*para*-.	
Fluorene	741 cm.$^{-1}$	4 : 4′-Dihydroxydiphenylmethane	816 cm.$^{-1}$
Diphenylene oxide	750 ,,	2 : 4′-Dihydroxydiphenylmethane	810 ,,
2 : 4′-Dihydroxydiphenylmethane	752 ,,	4 : 4′-Dihydroxydiphenylmethane	827 ,,
2 : 2′-Dihydroxydiphenylmethane	754 ,,		

Some compounds show simultaneously the mono- and di-substituted type, such as

	Mono.	*o*-Di.	*p*-Di.
p-Hydroxydiphenyl	755	—	830
o- ,, ,,	730	754	—

Polysubstituted benzenes include the following:

3-Hydroxymethyl-*p*-cresol (1 : 2 : 4)	815 cm.$^{-1}$
3 : 5-Bishydroxymethyl-*p*-cresol (1 : 2 : 3 : 5)	864 ,,
5-Hydroxymethyl-*o*-4-xylenol (1 : 2 : 4 : 5)	856 ,,

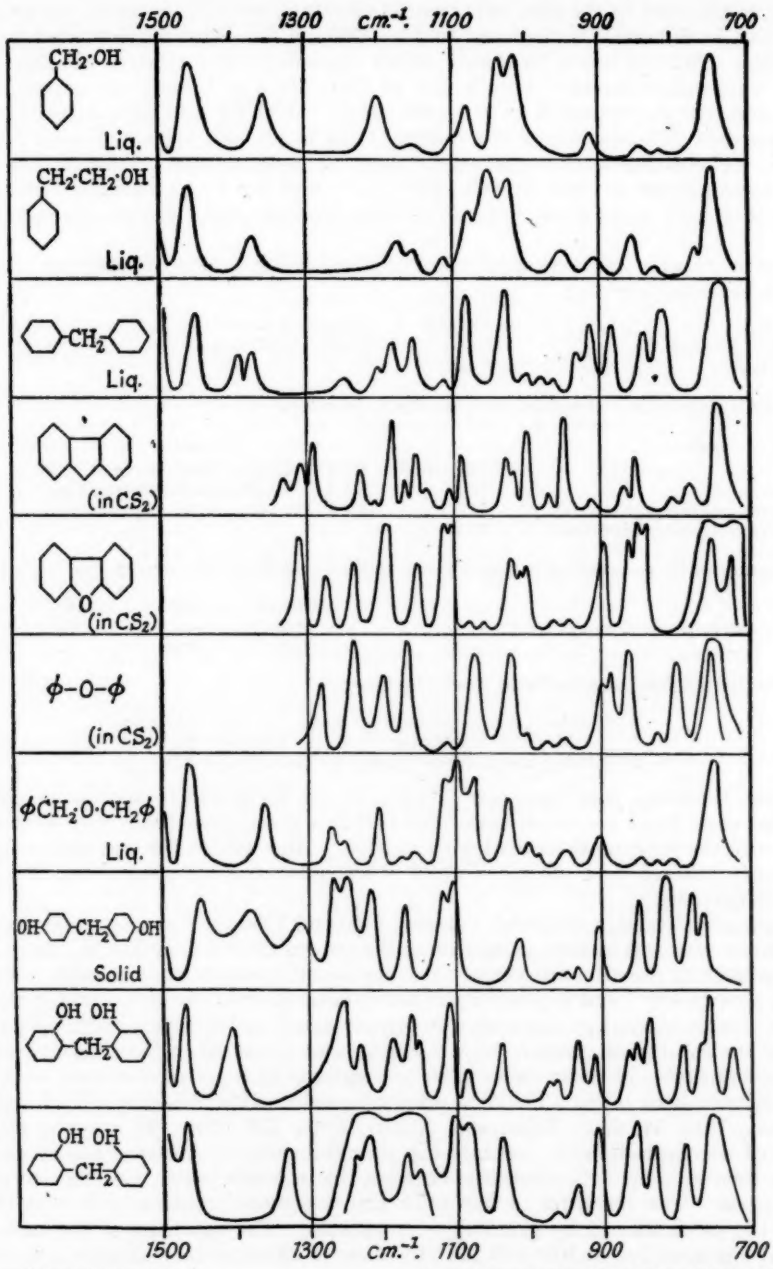
It is clear, therefore, that these correlation rules are fairly widely applicable, although it is obvious that since there are small variations within a given class there may in some cases be ambiguity and the rules must be used with caution. Also, whilst the correlations do not seem to be seriously affected by a change of state of the substance being measured, this possibility must not be excluded.

It is impossible to assign the bands between 1000 and 1500 cm.$^{-1}$ to particular normal modes, although this region will include vibrations of the groups C–O–C, C–O–H, CH_2, and CH_3, as well as of the skeleton of the aromatic rings. It is, however, apparent that in these cases the exact position of a particular band depends upon the environment of the group within the molecule. It is hoped shortly to explore this region in greater detail under higher resolving power.

Some of the substances given in Figs. 1 and 2 were measured in the solid and in the liquid state, or in solution. In some cases there are striking changes of spectrum with change of state, which have been noted already in other connexions (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 260; Thompson, *Nature*, 1946, **158**, 234). In order to eliminate the possibility of decomposition on melting, the procedure was to measure the spectrum of the liquid first, then to allow it to crystallise between the rock-salt plates, and then to measure the solid film again. The spectrum of this solid film was also compared with that obtained by measuring the paste formed by grinding with paraffin. The spectrum of the monoalcohol of *m*-4-xylenol was measured at 100° and 250°, but showed no appreciable change, and other liquids showed no change of spectrum with temperature. It seems certain, therefore, that the marked changes of spectrum at the melting point must be connected with fresh influences which come into play in the arrangement of the molecules in the solid. The spectra of the solids usually show sharper bands than those of the liquids, and new bands appear which are absent with the latter. This whole problem is being examined more systematically, and a detailed consideration of the physical principles involved will therefore be deferred.

In Fig. 3 (Nos. 1, 2, 3, 4, 5) the spectra around 3 μ are shown of some simple *p*-substituted phenols in the solid state, and of dilute solutions in carbon tetrachloride. In the dilute solutions the normal sharp band of the hydroxyl group occurs at 3615 cm.$^{-1}$. With the solids, this band

FIG. 1.

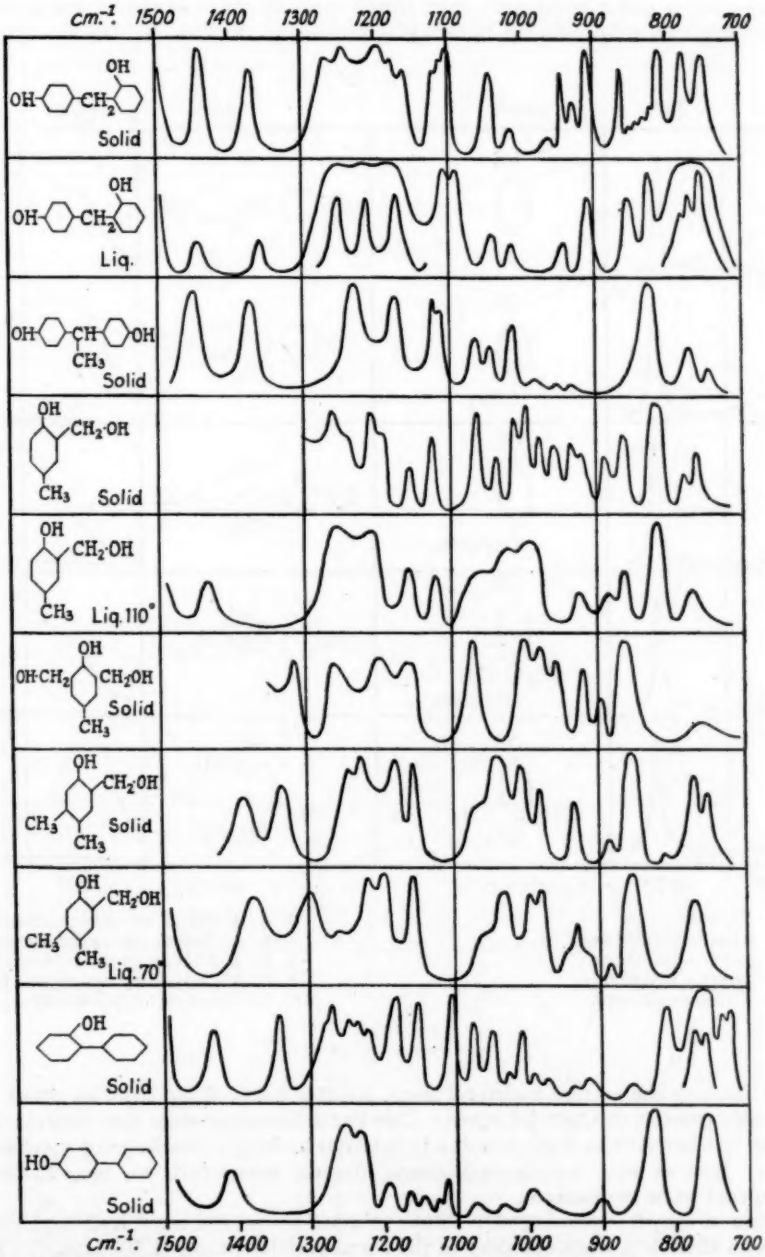


1. *Benzyl alcohol (liquid).*
2. *β-Phenylethyl alcohol (liquid).*
3. *Diphenylmethane (liquid).*
4. *Fluorene (in carbon disulphide).*
5. *Diphenylene oxide (in carbon disulphide).*
6. *Diphenyl ether (in carbon disulphide).*
7. *Dibenzyl ether (liquid).*
8. *4 : 4′-Dihydroxydiphenylmethane (solid).*
9. *2 : 2′-Dihydroxydiphenylmethane (solid).*
10. *2 : 2′-Dihydroxydiphenylmethane (liquid).*

is replaced by a broader band with centre at 3200—3250 cm.$^{-1}$, corresponding to the " bonded " hydroxyl group. With concentrated solutions, both the normal and the " association " band may appear simultaneously. These relationships correspond to those already examined by Fox and Martin, and others.

When there is a substituent in the *o*-position to the hydroxyl group (Fig. 4, Nos. 1, 2, 3, 4) the position of the " normal " hydroxyl group band in dilute solution is again at about 3615 cm.$^{-1}$, but the association band with the solids lies at rather higher frequencies than in the above cases of the simple *p*-substituted phenols. This implies that the screening of the hydroxyl

FIG. 2.

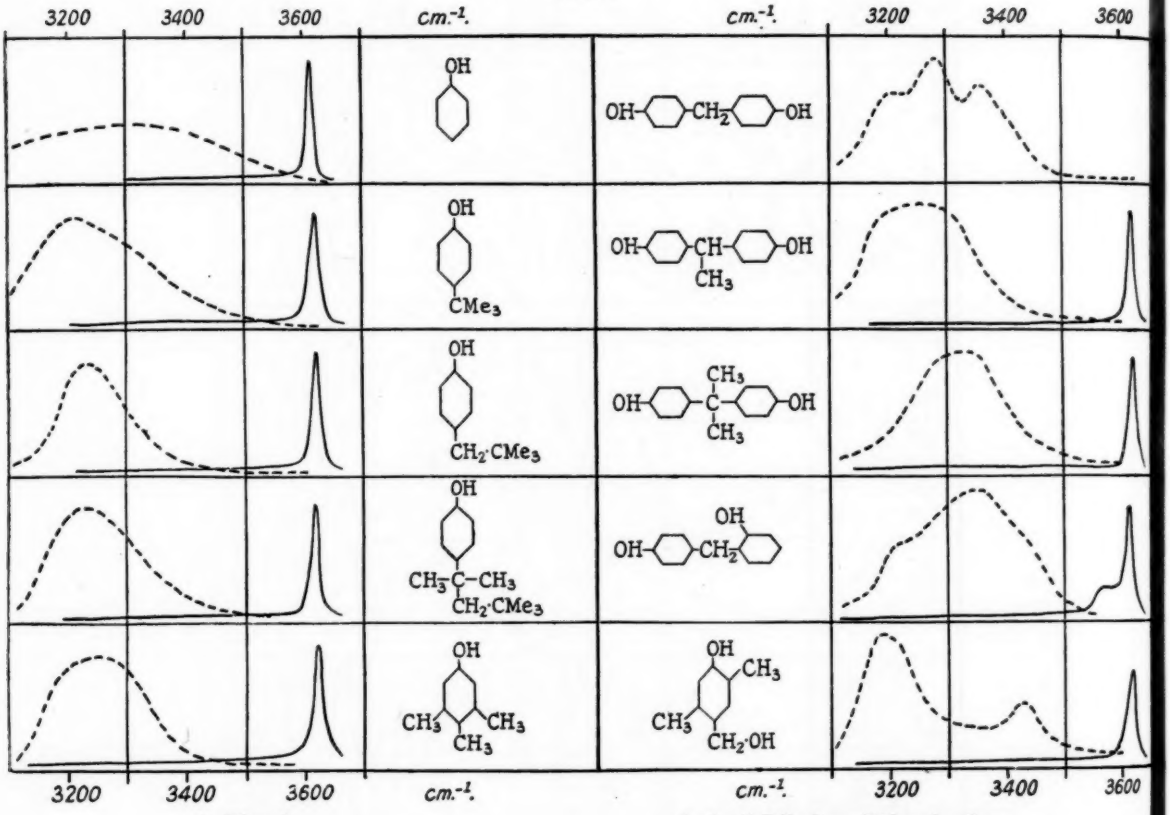


1. 2 : 4′-*Dihydroxydiphenylmethane* (*solid*).
2. 2 : 4′-*Dihydroxydiphenylmethane* (*liquid*).
3. 4 : 4′-*Dihydroxy-αα-diphenylethane* (*solid*).
4. 3-*Hydroxymethyl*-p-*cresol* (*solid*).
5. 3-*Hydroxymethyl*-p-*cresol* (*liquid*).
6. 3 : 5-*Bishydroxymethyl*-p-*cresol* (*solid*).
7. 5-*Hydroxymethyl*-o-4-*xylenol* (*solid*).
8. 5-*Hydroxymethyl*-o-4-*xylenol* (*liquid*).
9. 2-*Hydroxydiphenyl* (*solid*).
10. 4-*Hydroxydiphenyl* (*solid*).

group by the neighbouring groups decreases the strength of the hydrogen bridges which may be formed. With diphenylcarbinol and triphenylcarbinol (Fig. 4, Nos. 7, 8) this steric influence is well marked. In these connexions *o*-hydroxydiphenyl appears to be an exception, and will be discussed below.

When there are two hydroxyl groups in the molecule (Fig. 3, Nos. 6—10; Fig. 4, Nos. 6, 9—16) the dilute solutions again show the " normal " hydroxyl band at about 3615 cm.$^{-1}$, but in the solid state a given compound may simultaneously show several " association " bands. When there are two neighbouring hydroxyl groups (Fig. 4, Nos. 9—16) the dilute solutions

FIG. 3.



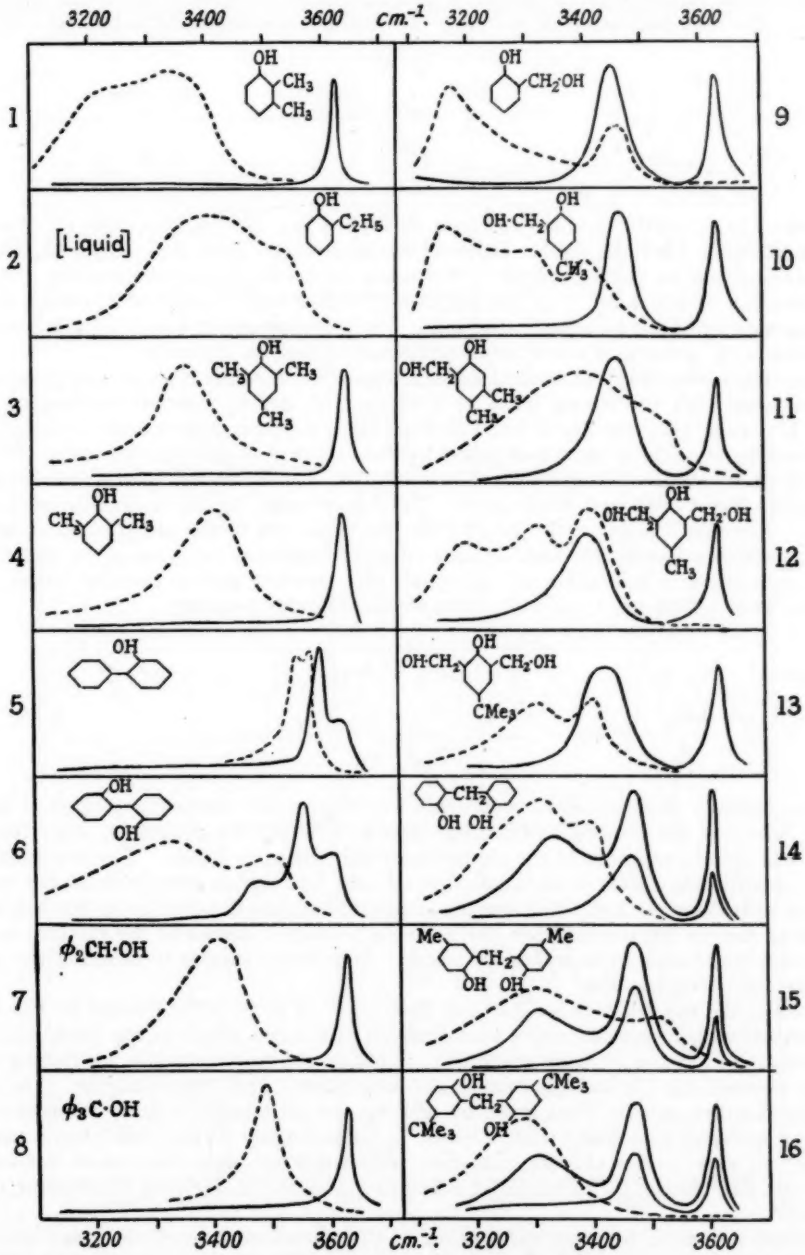
1. *Phenol.*
2. p-tert.-*Butylphenol.*
3. p-tert.-*Amylphenol.*
4. p-tert.-*Octylphenol.*
5. s.-*Hemimellitenol.*
6. 4 : 4′-*Dihydroxydiphenylmethane.*
7. 4 : 4′-*Dihydroxy-αα-diphenylethane.*
8. 4 : 4′-*Dihydroxy-ββ-diphenylpropane.*
9. 2 : 4′-*Dihydroxydiphenylmethane.*
10. 5-*Hydroxymethyl*-p-3-*xylenol.*

----- *solid.*
——— *solution in* CCl_4.

show, in addition to the normal hydroxyl band, another fairly sharp band at about 3450 cm.$^{-1}$, which generally persists in the solid state. This band is sharper than the customary " association " bands, but behaves as if it were due to internal hydrogen bonding not markedly affected by dilution. Just as with *o*-hydroxydiphenyl already mentioned, so, too, 2 : 2′-dihydroxydiphenyl appears to be anomalous.

In the case of *o*-hydroxydiphenyl, a dilute solution shows the main hydroxyl band at 3590 cm.$^{-1}$, although there is a weak shoulder in the usual position at about 3610 cm.$^{-1}$. In the solid a close doublet appears at 3560 cm.$^{-1}$. Reference to a scale model of the molecule suggests that the size of the OH group is such that the planes of the two aromatic rings may be slightly oblique to each other. In any case, however, the distance between the oxygen atom and the 2′-carbon atom is within the value which would allow of a hydrogen bond being formed of the

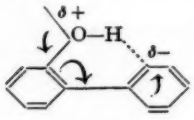
FIG. 4.



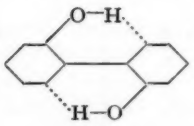
1. o-3-*Xylenol.*
2. o-*Ethylphenol.*
3. *Mesitol.*
4. m-2-*Xylenol.*
5. 2-*Hydroxydiphenyl.*
6. 2 : 2′-*Dihydroxydiphenyl.*
7. *Benzhydrol.*
8. *Triphenylcarbinol.*
9. o-*Hydroxybenzyl alcohol.*
10. 3-*Hydroxymethyl*-p-*cresol.*
11. 5-*Hydroxymethyl*-o-4-*xylenol.*
12. 3 : 5-*Bishydroxymethyl*-p-*cresol.*
13. 2 : 6-*Bishydroxymethyl*-p-tert.-*butylphenol.*
14. 2 : 2′-*Dihydroxydiphenylmethane.*
15. 2 : 2′-*Dihydroxy*-5 : 5′-*dimethyldiphenylmethane.*
16. 2 : 2′-*Dihydroxy*-5 : 5′-*di*-tert.-*butyldiphenylmethane.*

– – – – – *solid.*
——— *solution in* CCl_4.

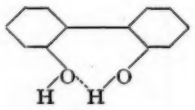
type –O–H····C–. In this particular case the formation of such a bond might be assisted by the fractional charge which the 2′-carbon atoms may acquire owing to electronic displacements depicted in (I). The formation of –C–H····O– bridges has been established by infra-red and



(I.)



(II.)

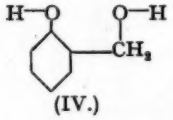


(III.)

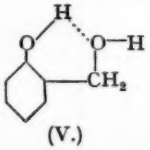
other methods (*e.g.*, Gordy, *J. Chem. Physics*, 1940, **8**, 170; 1941, **9**, 204, 215; *J. Amer. Chem. Soc.*, 1938, **60**, 605; 1941, **63**, 1094; Buswell, Rodebush and Roy, *ibid.*, 1938, **60**, 252), and it is not unreasonable to expect –O–H····C– bonds in favourable circumstances. If there is internal bonding of this kind, it is not surprising to find only a small shift of the absorption band on passing from the solution to the solid. In this connexion, too, it is worth noting that *o*-hydroxydiphenyl melts at a much lower temperature than its *p*-isomer.

2 : 2′-Dihydroxydiphenyl in dilute solutions shows some similarities to *o*-hydroxydiphenyl. It may be noted that the strong band at 3560 cm.$^{-1}$ is due to internal bonding of the type –O–H····C–, as in (II), the broad band at 3610 cm.$^{-1}$ to some unassociated hydroxyl groups, and the weak band at 3470 cm.$^{-1}$ to bonded hydroxyl group of the type shown in (III).

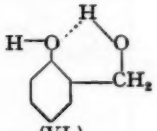
With dilute solutions of compounds containing two close hydroxyl groups, two sharp bands were found at about 3610 and 3450 cm.$^{-1}$. The former must be due to free hydroxyl groups as in (IV). Internal bonding as in (V) or (VI) may give rise to the sharp band at 3450 cm.$^{-1}$ which is sometimes hardly affected, or only slightly displaced, on passing to the solid. In the solid state there is indication of intermolecular bonding giving broader bands at lower frequencies (3200—3350 cm.$^{-1}$), as well as the intra-molecular bonding.



(IV.)



(V.)



(VI.)

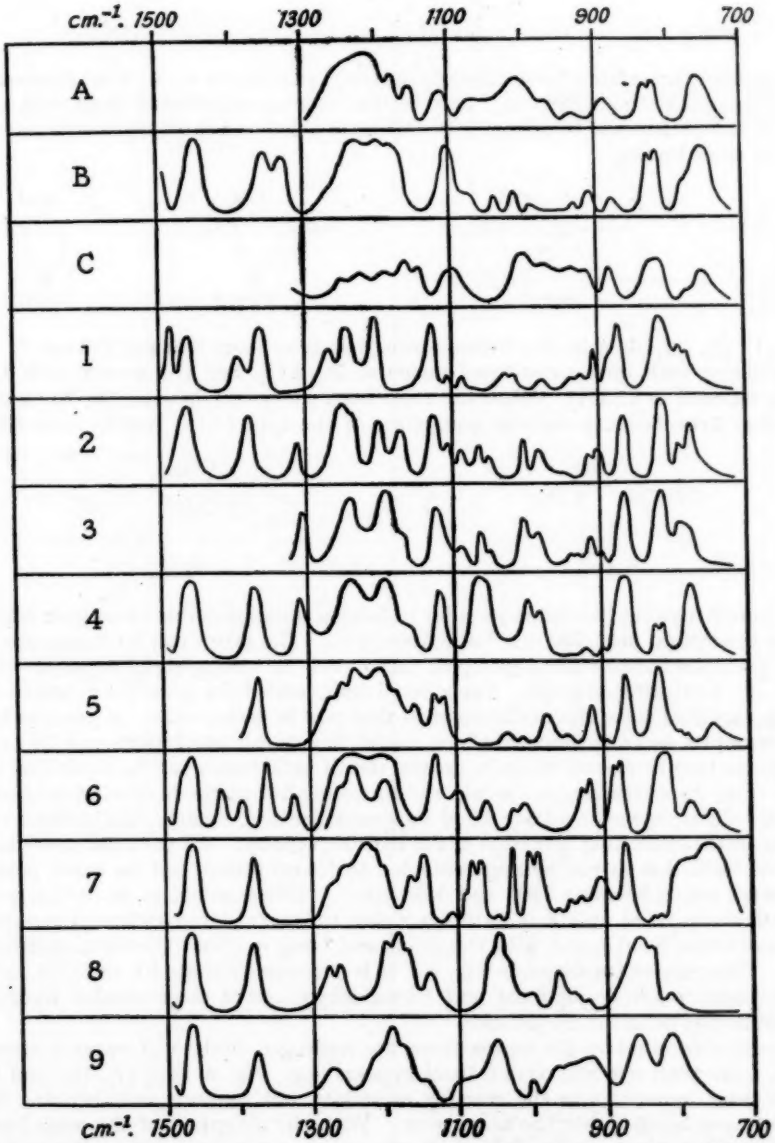
Some exploratory attempts have been made to measure the relative intensities of the bands due to the free and the bonded hydroxyl groups at different temperatures, since this should lead to a quantitative estimate of the strengths of the hydrogen bonds. The low boiling point of carbon tetrachloride makes it an unsuitable solvent, but carbon tetrabromide has been used in thickness up to 5 cm. at 3 μ. The spectra of *o*-hydroxybenzyl alcohol in carbon tetrachloride at 20°, and in carbon tetrabromide at 100°, show a profound change in the relative intensities of the free and the bonded hydroxyl group bands. It is hoped shortly to extend these measurements by an improved method.

Fig. 5 shows the spectra between 700 and 1500 cm.$^{-1}$ of some resins formed by the condensation of phenols with formaldehyde or acetaldehyde at various stages of the condensation, and there are examples of pairs of resins made from the same starting materials but having different physical properties, *e.g.* (2) and (3) from *p-tert.*-amylphenol and formaldehyde. The samples were measured either as solid films made by melting and allowing to solidify between rock salt plates, or by grinding to a paste with "Nujol." Undoubtedly a little free phenol must have been present in some of the starting materials, and there are signs that small amounts were present in the final resins. This must be taken into account in drawing conclusions from the measurements.

Clear differences exist between the spectra of the phenol–formaldehyde resins at different stages of condensation. In particular, the two-stage fusible resin differs from the one-stage resin in having a stronger band at about 1105 cm.$^{-1}$, and weaker absorption between 950 and 1050 cm.$^{-1}$. The two-stage infusible resin shows the band at 880 cm.$^{-1}$ relatively more strongly, and has intense absorption between 900 and 1000 cm.$^{-1}$. All the other resins show significant differences in the region 900—1500 cm.$^{-1}$. For example, (2) and (3), novolacs of different melting point made from *p-tert.*-amylphenol and formaldehyde, differ in the region 1100—1300 cm.$^{-1}$, and the resol (4) has a strong band near 1070 cm.$^{-1}$ which is probably connected with the $-CH_2 \cdot OH$ group. The differences between the spectra of (8) and (9) reflect the different nature of the xylenols used in their preparation.

The spectral differences in the range 700—900 cm.$^{-1}$ are especially important, since as already explained the intense bands in this region may be associated with C–H deformations of different kinds of substituted benzene nucleus. In the one-stage phenol–formaldehyde resin the band

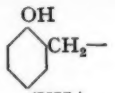
FIG. 5.

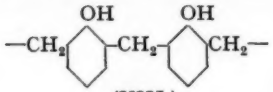


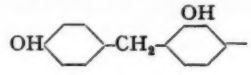
A. *Phenol–formaldehyde resin, one-stage.*
B. *Phenol–formaldehyde resin, two-stage, fusible.*
C. *Phenol–formaldehyde resin, two-stage, infusible.*
1. p-tert.-*Butylphenol–formaldehyde, novolac.*
2. p-tert.-*Amylphenol–formaldehyde, novolac.*
3. p-tert.-*Amylphenol–formaldehyde, high m.p. novolac.*
4. p-tert.-*Amylphenol–formaldehyde, resol.*
5. p-tert.-*Octylphenol–formaldehyde, novolac.*
6. p-tert.-*Butylphenol–acetaldehyde, novolac.*
7. p-α-*Phenylethylphenol–formaldehyde, novolac.*
8. *Xylenol–formaldehyde, high m.p. novolac.*
9. *Xylenol–formaldehyde, novolac.*

at 750—760 cm.$^{-1}$ will be due to *o*-substituted nuclei, and to any residual free phenol. Such *o*-substituted groups will presumably be as in (VII), the end groups of a chain, and the intensity of the band suggests that such groups are relatively so numerous that the chain length must be

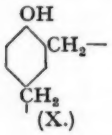
fairly short, say 4—8 aromatic nuclei. The weaker band at about 780 cm.$^{-1}$ in the two-stage resins is probably due to 1 : 2 : 3-substituted rings of the type (VIII). The bands at 815—

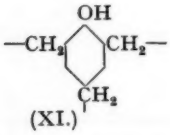

(VII.)

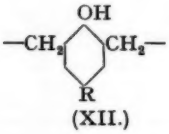

(VIII.)

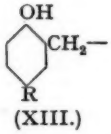

(IX.)

830 cm.$^{-1}$ probably arise from *p*-substituted rings such as (IX), or 1 : 2 : 4-substituted rings such as (X). The band at about 880 cm.$^{-1}$ may be due to tetra-substituted rings such as (XI), and it may be noted that in the two-stage infusible resin this band is strengthened, as would arise from further cross linking.

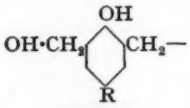

(X.)

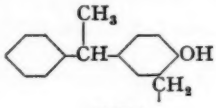

(XI.)


(XII.)


(XIII.)

Resins (1), (2), (3), (5), and (6) all show strong bands at about 820 and 870 cm.$^{-1}$. The latter can be correlated with tetra-substituted nuclei as in (XII), and the former with 1 : 2 : 4-substituted nuclei such as (XIII). With the resol from *p-tert.*-amylphenol (4), the weak band at 820 cm.$^{-1}$ may arise because the end groups are of the type (XIV), rather than (XIII). The


(XIV.)


(XV.)

resol from *p*-α-phenylethylphenol is peculiar in having no appreciable band near 820 cm.$^{-1}$, and has intense absorption near 750 cm.$^{-1}$ and 790 cm.$^{-1}$. The latter can be interpreted as arising from the monosubstituted phenyl group in (XV), and the strong shoulder at about 790 cm.$^{-1}$ from the 1 : 2 : 4-substituted rings. The xylenol resins also differ from the others in this region, as might be expected since the nuclei must in this case be either tetra- or penta-substituted.

These examples serve to illustrate how useful structural correlations can be made, but it would be premature to discuss them in greater detail until resins can be examined which have been made from purer starting materials and by controlled methods of condensation.

The resins differ, however, in one other important feature, namely, the position of the band near 3 μ due to the stretching vibration of the hydroxyl group. All the solid resins show a more or less broad band due to the hydrogen-bonded hydroxyl group, but its exact position varies in the different resins between 3200 and 3550 cm.$^{-1}$. Dilute solutions in carbon tetrachloride show a weak sharp band at about 3615 cm.$^{-1}$ due to unassociated hydroxyl groups, together with the association band found with the solids and lying in about the same position as in the latter case. The results are shown in Fig. 6. It is noteworthy that (10) and (11), both novolac resins made from *p-tert.*-octylphenol and formaldehyde, have their bonded hydroxyl group bands at noticeably different frequencies.

The results show that in the resins there are hydrogen bridges of varying strengths. In some cases, more than one association band appears [*e.g.*, Fig. 6, Nos. (7), (1), and (2)]. This might arise from impurities in the starting materials, but is more probably due to different types of hydrogen bond within the same resin. With the exception of the weak band at 3615 cm.$^{-1}$ in dilute solutions there is a close similarity between the spectra of a solid resin and of its solution. This suggests that the majority of the hydrogen bonds may be intramolecular, which would agree with the comparatively low melting points of these particular resins, and also with the inactivity of their hydroxyl groups towards diazomethane. If this is so, one factor in the "curing" of the resins might be a change from intra- to inter-molecular association. In the final heating intramolecular bonds may be opened, and larger complexes formed by inter-molecular association. Whilst such changes may only be one factor in the "curing" process, it might cause a considerable rise of melting point and hardness quite apart from that caused by further chemical condensations. The differences in the strengths of the hydrogen bonds in the solid novolacs are to some extent paralleled by differences in their physical properties.

This was well marked in the resins (10) and (11) shown in Fig. 6. A more exhaustive and controlled survey of this question is desirable.

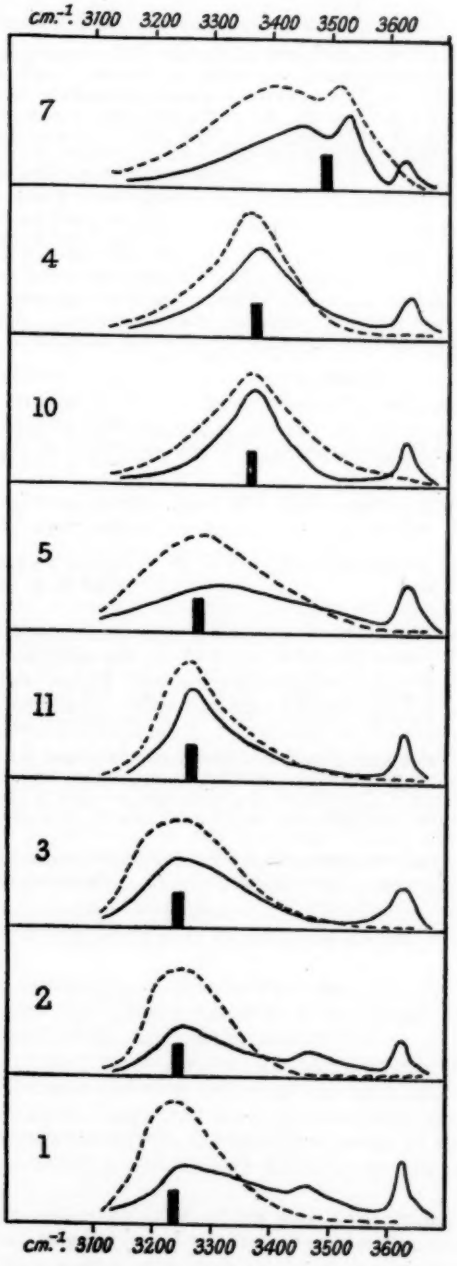


FIG. 6.

7. p-α-*Phenylethylphenol–formaldehyde, novolac.*
4. p-tert.-*Amylphenol–formaldehyde, resol.*
10. p-tert.-*Octylphenol–formaldehyde, novolac.*
5. p-tert.-*Octylphenol–formaldehyde, novolac.*
11. p-tert.-*Octylphenol–formaldehyde, novolac.*
3. p-tert.-*Amylphenol–formaldehyde, high m. p. novolac.*
2. p-tert.-*Amylphenol–formaldehyde, novolac.*
1. p-tert.-*Butylphenol–formaldehyde, novolac.*

– – – – – *solid.*
——— *solution in* CCl_4.

We are grateful to the Government Grant Committee of the Royal Society for a grant in aid of equipment, and to the Department of Scientific and Industrial Research for a Maintenance Grant.

THE PHYSICAL CHEMISTRY LABORATORY,
OXFORD.

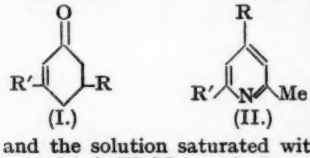
[*Received, November 6th,* 1946.]

NOTE.

2-cyclo*Hexenones from* 2-*Methylpyridines.*

By ARTHUR J. BIRCH.

DERIVATIVES of several methyl-2-*cyclo*hexenones were required for comparison with those obtained from the reduction products of methylanisoles and methyldimethylanilines (*J.*, 1944, 430; 1946, 593). Ketones of type (I; R′ = alkyl) have been obtained by the cyclisation of 1 : 5-diketones, but for the formation of type (I, R′ = H) the more difficultly accessible 1 : 5-keto-aldehydes are necessary (cf. Koetz and Steinhorst, *Annalen*, 1911, **379**, 20). Derivatives of both kinds of dicarbonyl compound have been obtained from 1 : 4-dihydropyridines (Shaw, *J.*, 1937, 300), and it has now been found that reduction of 2-methylpyridines with sodium and alcohol in liquid ammonia followed by refluxing with acid leads to hydrolysis of the dihydropyridine and cyclisation with direct formation of the *cyclo*hexenone.



(I.) (II.)

The 2-methylpyridine (10 g.) was reduced with sodium (5 g.) and alcohol (20 c.c.) in ammonia (150 c.c.) (see Birch, *J.*, 1946, 595), water (150 c.c.) added, the product isolated by ether extraction, and refluxed for 6 hours with sulphuric acid (*d* 1·84, 15 c.c.) and water (50 c.c.), and the solution saturated with ammonium sulphate and extracted with ether. The ether solution was dried (K_2CO_3) and the product distilled.

Pyridine.	*cyclo*Hexenone.	Derivatives.
2-Methyl- (II; R = R′ = H).	2- (I; R = R′ = H), b. p. 164—168°, 12%.	2 : 4-Dinitrophenylhydrazone, m. p. 164—165°.
2 : 4-Dimethyl- (II; R = Me, R′ = H).	5-Methyl-2- (II; R = Me, R′ = H),[1] b. p. 179—183°, 15%.	2 : 4-*Dinitrophenylhydrazone*,[2] m. p. 145—146°; semicarbazone,[3] m.p. 175—176°.
2 : 6-Dimethyl- (II; R = H, R′ = Me).	3-Methyl-2- (I; R = H, R′ = Me),[4] b.p. 194—197°, 17%.	2 : 4-Dinitrophenylhydrazone, m. p. 174°; semicarbazone, m. p. 200—202°.
2 : 4 : 6-Trimethyl- (II; R = R′ = Me).	3 : 5-Dimethyl-2- (I; R = R′ = Me),[5] b. p. 205—210°, 30%.	2 : 4-Dinitrophenylhydrazone, m. p. 163—164°; semicarbazone, m. p. 176—177°.

[1] Found: C, 76·4; H, 9·3. Calc. for $C_7H_{10}O$: C, 76·4; H, 9·1%.
[2] Found: C, 53·7; H, 4·8. $C_{13}H_{14}O_4N_4$ requires C, 53·7; H, 4·8%.
[3] Found: C, 57·5; H, 7·7. Calc. for $C_8H_{13}ON_3$: C, 57·5; H, 7·8%.
[4] Found: C, 76·1; H, 9·1. Calc. for $C_7H_{10}O$: C, 76·4; H, 9·1%.
[5] Found: C, 77·8; H, 9·5. Calc. for $C_8H_{12}O$: C, 77·5; H, 9·7%.

The yields of *cyclo*hexenones are poor, and the method has no advantage over the standard ones for their preparation in quantity, except where the alkypyridine is readily available and other methods are difficult, *e.g.*, 5-methyl-2-*cyclo*hexenone from 2 : 4-dimethylpyridine (cf. Koetz and Steinhorst, *loc. cit.*). For the preparation of small amounts of derivatives the method is rapid and convenient.

This work was carried out during the tenure of an I.C.I. Research Fellowship.—THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 19th*, 1946.]

Address on the Occasion of the Centenary Celebration of the Chemical Society.

By THE PRESIDENT, PROFESSOR C. N. HINSHELWOOD, M.A., Sc.D., D.Sc., F.R.S.

THE observance of anniversaries and centenaries is dictated by a deep-seated instinct. How far this in its turn is inspired by a feeling for the magic of numbers and awe at the vast cyclical processes of Nature, I do not know, but, however that may be, these recurrent occasions for retrospect and prospect are assuredly felt to be significant and moving.

The character of the thoughts and emotions which they arouse will in some measure depend upon the attitude towards history adopted by the participants. To some, history is as a play that is ended : to others, as a chart on which they hope to read the future from the past. But to everyone, I suppose, the centenary of a scientific society must bring a message of some kind.

There are few dramas as enthralling as the struggle for the secrets of reluctant Nature, and few fields in which the future beckons so insistently as in that of scientific thought.

We are celebrating the centenary, not of a discovery, not of a person, but of a Society, and this circumstance reminds us that thoughts and inventions are in a considerable measure the products of particular historical settings. For our purpose, therefore, we cannot reflect upon the history of chemistry in the past century in England, or speculate upon its probable future, except in relation to the people who made it and are making it, and to the general conditions of their lives.

Not only does the pious memory of our Founders, benefactors, and predecessors (both the recognised and the unrecognised great men) bid us consider the human as well as the purely intellectual story, but it is doubtful whether any other approach would be more than an abstraction with the limited validity which abstractions have.

You see what deep philosophical questions are raised by the major theme : the relation of the scientific and the humane; the nature of history and the possibility of extrapolation and prediction; piety towards the past, expectations from and duties toward the future. I feel called upon to remind you of these themes, even though I cannot possibly do justice to them.

The Chemical Society was founded in the year 1841. The England in which it came into being stood on the threshold of one of its greatest eras of expansion, but no one at the time could know of this, and to many the prospect must have appeared sombre and even fuller of uncertainties than that which confronts us today. The dislocations caused by the Industrial Revolution were all too obvious, but the fruits of progress were still to be gathered. The lot of the impoverished manual workers was wretched in the extreme, the scandals of child labour in coal mines, potteries, and other industries were coming to light, but the Factory Acts were not yet passed, the agitation and distress connected with the Corn Laws coloured the political scene, and the demand of workers for a better mode of life expressed itself in the Chartist movement and broke forth into riots which to many people suggested that society was on the verge of revolution and disruption.

Queen Victoria was on the throne, but the splendours of her era were yet to be, and the great movements of her time would only have been discernible to those of unusual penetration. The worst social conditions depicted in the writings of Dickens still prevailed.

There was nothing in the obvious character of the time to announce a period of intellectual flowering, and yet it was just then that many learned societies, including our own, came into being. Scientific studies in England were hardly in any clear way the product of their age, and sprang more from the learned curiosity of amateurs than from the conscious needs of society. There were practically no laboratories for chemical research, and little or no University instruction in chemistry.

The chemical stage was set as follows. In 1841, the time which had elapsed since the " chemical revolution " of Lavoisier was almost exactly equal to that from the discovery of radioactivity to the present day. Chemistry as a science was then as old as is now the new nuclear alchemy upon which we believe the future so largely to depend. It is difficult today for a scientifically educated person to realise how profound was the change of thought which followed the publication of the Lavoisier treatise. It represented a complete philosophical re-orientation of ideas on the nature of substance. Two Englishmen in very different ways had played parts of the first magnitude. Priestley, whose house was wrecked by a mob, had made the discovery which opened the way for Lavoisier, and Dalton, living in an obscurity which astonished his foreign visitors, had formulated the theory upon which all future development was to depend.

Between the time of Dalton and the foundation of the Chemical Society the great forward sweep of organic chemistry had begun, but in this the English school had played little part, as was explicable in a country which tended to produce a few of the finest flowers of science, art, and literature without any very vigorous general growth of leaf and root. At the moment of our foundation Dalton was still alive, but Liebig, who visited England at about this time, found little in the world of chemistry to inspire him. Yet Faraday was at the height of his powers and his great work on the laws of electrolytic action was already accomplished. Its full implications were far from obvious to his contemporaries, and indeed the confusions which Avogadro's paper of 1811 might have cleared away still clouded chemistry. On the Continent the great battle between the rival interpretations of the structure of organic compounds was at its height.

At about this time much was being done in England to lay the foundations of physical chemistry, not only by Faraday with his work on the liquefaction of gases and on electrochemistry, but also by the original and versatile Thomas Graham, first President of the Chemical Society.

Such was the chemical scene at the time of our foundation.

Let us now, after the manner of the dramatist, raise the curtain at successive intervals of a generation and see what transformations have been brought about.

1861, twenty years after the foundation, was, as it happens, the year of Prince Albert's death and of the outbreak of the American Civil War. The early dislocations caused by the Industrial Revolution were now largely righted, the conditions of labour had improved, steamships and railways were in rapid development, the era of prosperity symbolised by the Great Exhibition of 1851 was well launched, and the great intellectual movements of the Victorian age were under way. Herbert Spencer's advocacy of scientific education sought to justify in theory what the foundation of the College of Chemistry in 1847, Owens College, Manchester, in 1851, and the Oxford laboratories in 1861 were gradually implementing in practice. " The Origin of Species " had appeared in 1859, and the materialist trend of thought was evident. Chemistry had seen two decades of steady progress but had been on the whole unshaken by revolutionary changes. Cannizzaro's paper of 1858 had removed one of the major obscurities, and Frankland and Kekulé had placed structural chemistry on a firm foundation. In this country Hofmann, Mansfield, Williamson, and Frankland are seen among the outstanding figures of the period. Chemistry in England was still mainly the affair of the amateur. Indeed, in 1867 the only technical education in Leeds with its quarter of a million inhabitants was provided by one teacher who worked in a cellar and held a class in chemistry, receiving a grant of £11 a year for the purpose. Nevertheless the *Journal of the Chemical Society* from its early years had attracted contributions from the eminent chemists of the Continent, and the names of Liebig and Bunsen are in evidence.

Another twenty years pass and many momentous changes have occurred. The historical background shows political democracy in England in full stride with widened franchise and a sweeping increase in general literacy: it shows the decline of agriculture in its most disastrous phase, and the British primacy in the manufacturing export trade just about to decline from its height. The early signs of major world troubles are already discernible: the rank weeds of bureaucracy are breaking through the soil, and since 1870 the world has learnt from Prussia that war on the national scale has possibilities hitherto unexploited. The curse of conscription already lies on Europe. Disraeli has died, and Karl Marx lives in London. In some respects the Victorian age has passed its zenith, and some of the brightest stars have set: Dickens, Mill, and Clark Maxwell are gone, and Darwin's work is over. Although there have been important events such as the founding of the Cavendish laboratory in 1871, the position of scientific studies in the Universities is still feeble, and even now the great discoveries and inventions continue to come from men who are self-taught and have received little formal training.

Some of the great trends of chemistry are reflected in our *Journal*. One of the most splendid phenomena had been the flowering of the great tree of organic chemistry. To this science the contribution of England was honourable but limited. At the time in question the great name of Perkin appears currently, first the father, then the son. The science of physical chemistry is well launched, and perhaps the papers of Harcourt and Esson on the " Course of Chemical Change " are among the most characteristic of the contributions from this country. We must note the immense clarification which chemistry had by now received from the Periodic Law, observing with satisfaction that Newlands had done so much to initiate this by a paper read to the Chemical Society in 1866, but with regret that this paper was never published.

The *Journal* of the year 1881 is interesting. Boron hydride is described, while experiments on the synthesis of ammonia and discussions of absorption spectra show the approach of modern

times. But one publication above all shines like a beacon. This is the great Faraday lecture of Helmholtz, where for the first time the full implications of Faraday's laws are revealed and the way is opened for the whole modern electronic theory.

As an example of the delay which may attend the exploitation of valuable discoveries a passage in the Presidential Address of Roscoe in this year speaks for itself. "The researches of Captain Abney have been continued with conspicuous succcess, and have given birth to a discovery of the highest interest and of the greatest possible promise. This is no less than a distinct physical test of the existence in organic compounds of the organic radicals, and a means of recognising the chemical structure of an organic compound by means of the spectroscope. This result, which naturally opens out an entirely new field for investigation, and effects for the organic metals that which ordinary high temperature spectrum analysis does for the inorganic metals, is accomplished by photographing the absorption spectra of organic compounds in the infra-red part of the spectrum. In these invisible portions, characteristic and distinct absorption lines and bands occur for each organic radical. . . . This investigation is still in its infancy, but one of greater importance to chemists has seldom, if ever, been communicated to the Society."

The next scene presents a mottled picture of sun and shade. In 1901 the death of Queen Victoria symbolised the end of an epoch. It was a time of intellectual and social unrest and uncertainty: agriculture had collapsed, industrial struggles had acquired a new bitterness, the tide of the new popular journalism was rising in a strong flood, and the administrative machinery of the country was elaborated beyond what had ever been known. Some trade prosperity and the residues of a romantic imperialism imparted their diverse glamours, and a brilliant Court was about to lend an appearance of solidity to an age which the first German War was destined to bring to a catastrophic end.

By this time the health of chemistry in Britain was much more robust, and schools of research were gradually coming into being in many of the Universities. Tilden in 1904 told the Chemical Society that he considered the science to be flourishing. A glance at the *Journal* of 1901 certainly shows a great variety of activities, which range over investigations on alkaloids, bacterial actions, optically active nitrogen compounds, absorption spectra, and the synthesis of methane. A paper by Lapworth marks the beginning of that detailed interpretation of the inner mechanism of reactions which has been one of the great British contributions to organic chemistry in the present century. It is indeed appropriate that the Faraday lecture to be given during the present celebrations is devoted to the exposition of this powerful theme.

Radioactivity had been discovered in 1896 by Becquerel, and in 1902 the first of Rutherford's great contributions makes its appearance in the *Journal*. A measure of the excitement of the times is conveyed by the words at the end of the second contribution of Rutherford and Soddy:

> "Nothing can yet be stated of the mechanism of the changes involved, but whatever view is ultimately adopted it seems not unreasonable to hope that radioactivity affords the means of obtaining information of processes occurring within the chemical atom."

The transformation by 1921 was colossal indeed in every aspect of life: profound political changes, an unprecedented degree of mechanism, and all the febrile aftermath of what then counted as the greatest war in history. People were more conscious than ever before of international and economic problems. The scene shifts from a national stage to a world stage.

The war of 1914—1918 had brought profound changes to British chemistry. It has often been called the chemist's war. Unprecedented needs of explosives, chemical warfare agents, and other products of industry had forced an improvised expansion, which, by a fortunate dispensation of providence, gradually merged into an orderly and continued evolution. In the following decade there is a history, which may be followed with a degree of sober satisfaction, of the creation of a new chemical industry, of the expansion of University research, of the founding of research institutes, and, not least, of the establishment of the most excellent relations between industrial and academic chemistry. These are one of the happiest auguries for our uncertain future.

Taking a glance at some of the subjects represented in the *Journal* of 1921, we find, in the first place, papers belonging to the aftermath of the chemist's war: on explosives and mustard gas, and on the sorption of gases: we are reminded of a major revolution in science by Aston's lecture on mass spectra. On the physical side, colloidal electrolytes, heterogeneous catalysis, and photochemistry are coming into prominence, and Brönsted's paper on salt effects typifies not only the transition from the older to the newer theories of solution, but also the abiding international character of our chemical literature. On the organic side, Perkin's papers on the

alkaloids, harmine and harmaline, belong to the culmination of one great tradition in organic chemistry, while a newer tradition, that of studying function as well as structure and of bringing physical ideas into intimate relation with the study of organic substances, is illustrated by papers on the influence of substituents on the character of benzene compounds and by a series of Ingold's early papers on questions of reactivity. Vernon's work on tellurium derivatives reminds us of the contributions which this country has made to stereochemical problems, especially through the researches of Mills, past President of the Chemical Society.

If we pursue our theatrical fancy to the end and raise the curtain for a last time on the actual centenary date of 1941, it discloses a scene of chaos and destruction. Two decades of fruitful progress seem to have been brought to a tragic end. In some ways the two decades had been among the most productive that chemistry had known. The constitution of natural products had been brilliantly revealed, and in this connexion the names of two Presidents of the Society—Haworth and Robinson—are outstanding. Modern theories of valency had brought an immense clarification into the whole system of inorganic chemistry: the subtleties of organic behaviour had been penetrated, and the intimate mechanism of chemical changes in general stood largely revealed. There had been a powerful cross-fertilisation of chemistry with physics and mathematics. And on the human side the developments were no less vigorous: vastly increased support of research in the Universities, a flood tide of advance in the chemical industry, and, not least, the growth of co-operation between the centres of pure science on the one hand and the great industries on the other, which was of incalculable significance.

As I have remarked, the way in which all this is assessed depends upon a philosophical attitude. One view of history sees the course of human affairs as a chaotic sequence of accidents, the results of unpredictable and indeed often unknowable contingencies: the other sees an orderly and inevitable flow of events in well-marked channels. In that great work "War and Peace" Tolstoy defends and illustrates the second thesis, discounting the influence of great men, and maintaining passionately that the fate of nations evolves naturally out of their essential nature.

All men of science are familiar with those controversies in which the arguments on both sides seem unanswerable: and they know that in the end the contending parties are realised to have seen not truth and falsehood but two aspects of a larger whole. A scientific analogy helps to resolve the conflict about the nature of history.

The evolution of material systems is governed both by those thermodynamic factors which determine equilibria and define the extent and direction of possible changes, and, differently but equally powerfully, by the kinetic factors which determine when and where the changes are initiated and with what speed they progress. The former depend upon average conditions such as temperature and pressure, the latter upon chance fluctuations of energy, highly localised and intense departures from the average. Without these exceptional events the system remains inert. But on the other hand, no fluctuation, however violent, causes its evolution in a direction different from that required by the thermodynamic state. So it may well be in affairs: the exceptional event, the rise of the great man of thought or action, determines time and location, but, for the exceptional to take effect, the average must be in a condition to respond.

In the survey of the century, therefore, one may try to discern the essential trends, to which great events and personalities are related more as occasions than as causes.

As far as chemistry is concerned the history of at any rate the first half of the century has been very much the affair of the individual. The great names—Davy, Faraday, Dalton, Graham, Newlands, Frankland, Perkin—do not seem to bear any special relation to their environment, and might seem to support the purely sporadic view of history. And yet certain general currents are discernible in the contribution from this country. Perhaps one of the deepest and strongest has been the evolution based upon an intuitive sense of the electrical nature of matter. By much more than a play of fancy a genealogy can be traced, through Davy who found the key to the phenomena of polar combination, Faraday, Crookes whose instinct guided him to the study of "radiant matter", Townsend and J. J. Thomson who infuse new blood from physics, to the modern schools of Lapworth, Robinson, and Ingold, who have carried the electrical conception into the subtlest regions of organic chemistry. Nor should I omit in this connexion to mention the scholarly studies of Sidgwick, another past President of the Society, which have done so much to clarify the vast field of inorganic chemistry. This line will almost certainly continue, but how, or where, is as indeterminate as the position of a single electron in an atom.

A collateral line is formed by those who, speculating on the nature of matter, were vouchsafed a glimpse of a promised land into which they did not enter fully—Prout, Newlands, Crookes.

The final conquest of that land came only when the armies of physics and of chemistry joined forces in the victorious advance of Rutherford and Soddy, Rayleigh and Ramsay, J. J. Thomson, Aston and Moseley.

In contrast with the imaginative quality of these men, another of our strongest traditions has been that of empirical observation, unguided by much in the way of theory. This has expressed and illustrated both a national strength and a national weakness. From the days of Priestley onwards, it has led to factual discoveries of the first importance, and produced experimenters second to none in such men as Dewar, Dixon, and Bone, but it has not created schools, and its positive achievements have occasionally been lessened by a mistrust of theory so healthy as almost to discourage understanding. But the impact of the two opposing schools has been unquestionably fruitful, and has sometimes added to the gaiety of nations.

Other recurrent themes can be traced throughout the century: on the one hand a sense of the mystery and wonder of chemical change, and on the other a joy in precise measurement for its own sake—two contrasted but equally important motives in the development of physical chemistry, which reflect the blend of the romantic and the practical in the make-up of so many Englishmen. Affinities could be traced throughout the period, as between the work of Graham and that of Berkeley and Hartley, or between the spirit of Harcourt and Esson and that of various modern schools. And yet, the purely personal character of much of the great work could equally well be illustrated by innumerable examples, such as Perkin's famous discovery of mauve, Dewar's observations on specific heats at low temperatures, or Crookes's studies of the rare earths.

The truth is, I think, that the more easily distinguishable threads have been woven more by what is common in the intellectual make-up of the people, than by a direct and conscious tradition. There are men who, placed in almost any circumstances, will mould them to something great, and it is such men predominantly whom we have to commemorate, at any rate in all but the last two decades of the century. The breeding of such men is not likely to change in any rapid way, but the nature of the society into which they are born is changing before our eyes.

One of the unmistakable trends of the past century has been the successive decline of different aspects of individualism: the independent craftsman, the aristocratic politician, the empire-building explorer all departed from the scene. In science a similar trend has been visible though at a lag of several decades. At the time of our foundation the stage is dominated by the amateur, whether a Cavendish or a Faraday: later the individual is more and more frequently dependent upon the University or technical college, small and independent but none the less a community. Then the great research associations appear and the State subsidy becomes indispensable. Two great wars intensified and accelerated the collective process in the world of science until today we are faced with the problems presented by vast industrial research laboratories and by state enterprises undertaking work which is inconceivable without the co-ordinated efforts of hundreds of men of science. The great question is: what is to be the fate of the individual in the world which has emerged?

In this matter something of an ideological battle has been engaged, and since the question is one of moment for the future of an independent scientific society, I propose to say a little about it, in as objective a manner as possible.

May I, for this purpose, introduce an analogy between human affairs and certain scientific laws? The particles composing matter are endowed with individual motions which would lead to complete chaos but for attractive forces constraining them at times into orderly configurations. The two conflicting tendencies are, of course, what men of science know as the entropy factor and the energy factor. It is the balance between the two which governs all the rich complexity of chemistry and physics, and determines that measure of effective action called free energy. Were there maximum entropy and complete chaos the world of phenomena would be much the poorer, but were there the rigid constraint which the energy factor alone would impose things would be as bad or worse. Nobody who has thought about science can fail to admire the art with which Nature interweaves her two great themes. When molecular chaos is set in order it is only at a price, but price and value are astutely bargained. So it must be in human affairs.

Complete individualism means chaos, which is only given form by something analogous to an energy factor—by State compulsion, or by powerful emotional forces. If any of these controls are applied too vigorously the result is order indeed but the order of utter stagnation. Just as Nature strikes her subtle balance, so it must be here. Nothing is less fruitful than doctrinaire argument about freedom and planning. The vast achievements of military regimentation in

wartime have been cited as examples for peace, but in this it is forgotten that results in limited spheres have had to be bought with an utter disregard of cost, whether of money, happiness, or life.

The problem is not to propound facile doctrines, but by hard and detailed thinking in every possible sphere to find those mechanisms and those techniques which in combination lead to the greatest measure of effective action.

A hundred years ago we saw an individualist society faced with the task of controlling the industrial revolution : at the beginning of a new century we face a task which seems even greater, that of preventing an organised society from turning individuals into slaves. The problem involves the relation of the State to science, of the industries to the Universities, the organisation of research laboratories, and indeed the relation of every man of science to the laboratory in which he works and to the science as a whole.

Those who call themselves planners are often, I think, not conscious enough of the art and effort involved in large-scale action. Even with the most admirable motives and goals, operative complexity often brings frustration. There is need for a complete new science, a kind of biological and psychological statistical mechanics to clarify these matters. The beginnings of it exist. Indeed we have seen one gigantic manifestation of directed human activity in the evil arts of the late rulers of Germany, whose ingenious mechanisms were applied in opposition to truth and justice but might have been used to better ends.

This thesis will be accepted readily enough by the exponents of what are now called social studies, but we may be told that the organisation of affairs must be placed in the hands of specially trained humanists, and that the scientific man should be confined to the rôle of an advisory expert. Such a tradition has of course tended to grow up in some of the public services. But one can say with conviction that its persistence will be unfortunate and its extension disastrous. It is like a separation of the heart from the brain and of the mind from the body. The man of science must himself handle the human problems, and, in scientific affairs, nobody but the man of science can do it. On the whole the Universities and the great chemical industries are aware of this, and the excellent relations which have been growing up between them will exert a powerful influence for good, and are of happy augury. But eternal vigilance is the price of these things. At every level in every organisation where men are engaged in scientific pursuits those in charge must continue to wrestle with the problems of combining liberty with order to the end of finding that course which is humanly as well as technically the most effective.

One very welcome sign of the past few years has been the increasing number of scientific papers published from the chemical industry. These are clear and welcome evidence that the leaders of that industry are showing understanding of the intellectual needs of the men who serve it. One can only hope that the whips of commercial secrecy will not be succeeded by the scorpions of military security.

Looking to the future of chemical research, one can confidently foresee an era of great technical progress. The powerful organisations which will ensure this are already in operation. The relevant problems of pure science will also be explored on a scale which has hitherto been undreamt of. Such matters as thermodynamic and kinetic studies on polymers, biological studies on chemotherapeutic agents, and scores of others could be cited to show how the approach is changing from the sporadic and the amateur to the thorough and the professional. All this leads to new knowledge of inestimable value, and in this field also progress seems assured.

But of that most important kind of new knowledge, that which does not seem to relate to any existing field, it is harder to speak on the basis of anything but faith. And yet in this knowledge lies the true seed of the future. It will come only from the least conforming of minds, and the discoveries of the greatest ultimate moment are the least likely to have been favoured by official encouragement or support. They must be like the flowers of the poet

> " daffodils,
> That come before the swallow dares, and take
> The winds of March with beauty."

We may well ask whether the winds of future Marches may not be more intolerant than those of the past.

There is no royal road to be followed into the future. In the scientific and social history of the past century the picture has been one of light and shade, ebb and flow, and enormous uncertainties crowned by miraculous progress. On this scene men of all kinds have laboured for the science of chemistry. Today we honour them. There is no reason to suppose that

their qualities have not been inherited. The stage is changed and the parts are different, but the actors are very much the same.

It is still the individual who really counts, but his problems are different. Faraday's genius overcame lack of education and lack of facilities. These are handicaps from which he would be very unlikely to suffer today. The Faraday of tomorrow will have by his own methods to break through the trammels of an over-organised society: and for this it may well be that he will need something more of the quality of a Nelson.

Nothing has ever yet contained the great river of knowledge. Though Archimedes was slain, Galileo persecuted, and Lavoisier condemned, it has flowed over or around every obstacle which stupidity, indifference, or malevolence have created.

In the old eastern story a debate arises as to what is the strongest thing in the world, and in the end this is recognised to be the truth. "As for the truth it endureth and is always strong: it liveth and conquereth for evermore. . . . Great is truth and mighty above all things." Whatever clouds may seem to lower over the new century, this is the great light which shines on it.

But this faith does not obviate the necessity for continuous detailed effort. If it is based upon an extrapolation from the past, that past is one in which people were ready to struggle and endure. It is incumbent on us to consider what stands before our Society and what policies that Society should pursue.

There is one which stands in the centre of and indeed includes all other policies, and that is to maintain the prestige of chemistry as a pure science. It is right that the Chemical Society should occupy a central position in the world of chemistry. I have referred to the increasing complexity of this world, with its multiplicity of organisations. But by common consent new knowledge is the life blood of it all, and the heart should be the Chemical Society itself. Of the relations between the great chemical industry and the Universities I have already spoken, and gratitude must be expressed for the humane policy of so many leaders of that industry. But it remains for the younger chemists in it to take an ever more active part in the publication and discussion of new knowledge. Provision for this is one of those problems where the scientific and the humane are inseparable.

Relations between chemistry and its neighbour sciences—physics, mathematics, and biology—are now so close that the frontiers are practically abolished and the joint discussion of common problems will be of increasing importance.

All this raises a practical question of the first magnitude, that of adequate facilities for meeting. I feel a little ashamed that on this great occasion we should receive our guests in alien halls, however hospitable they may be. I should like to hope that before long a statesmanlike solution to this problem will have been found.

Important as buildings may be, our publications are still more so, and in the eyes of posterity the Society of today will be judged more by the quality of the work which it publishes than by any other criterion. As Shakespeare tells us, the immortality conferred by black ink is greater than that of gates of steel or rocks impregnable. It has been a sad economy which has lavished money upon so many objects while neglecting the means of scientific publication. We must continue to struggle against this unhappy policy and hope that it will pass, never to return.

Among the traditions upon which we look back with pride is that of the international character of the Society. I am happy to say that as the result of a special Centenary Appeal for the purpose this valuable element in our activity will be strengthened, and that we now have the means of bringing foreign men of science to take part more often and more fully in our doings. There can be no question of the great benefit which chemists in this country will derive from the arrangement.

And now to the conclusion of the whole matter. What the Society is and must continue above all else to be is a fellowship of those who share the love of chemistry, that most splendid child of intellect and art. Chemistry provides not only a mental discipline, but an adventure and an æsthetic experience. Its followers seek to know the hidden causes which underlie the transformations of our changing world, to learn the essence of the rose's colour, the lilac's fragrance, and the oak's tenacity, and to understand the secret paths by which the sunlight and the air create these wonders.

And to this knowledge they attach an absolute value, that of truth and beauty. The vision of Nature yields the secret of power and wealth, and for this it may be sought by many. But it is revealed only to those who seek it for itself. Its pursuit has united the predecessors whom we commemorate: it will unite our successors for as long as the spirit of man endures.

*A Century of Chemistry.**

A Lecture delivered on February 19th, 1947, at a Joint Meeting of the Royal Society of Arts and the Chemical Society to commemorate the Centenary of the Foundation of the Chemical Society.

By Sir Harold Hartley, K.C.V.O., M.C., F.R.S.

This evening Fellows of the Chemical Society have made a pilgrimage, not, it is true, a very long or hazardous one, although in this year of grace 1947 we shall return by torchlight, to John Street, Adelphi, to the Royal Society of Arts, the birthplace of our Society. We have come like the pilgrims of old, who made much longer journeys, in a spirit of piety to the place that holds such a high place in our memories, to pay our homage to the Society that gave us hospitality for our first meetings. It was on February 23rd, 1841, thanks to the initiative of Robert Warington and the kindness of his friend Arthur Aikin, formerly the Secretary of the Society of Arts, that twenty-five chemists, including Aikin, met in this building to consider founding a Chemical Society, and here its first regular meeting took place on March 30th, 1841.

The Society of Arts had been established for nearly a century, and its Secretary Aikin was a very remarkable man. He had been one of the founders of the Geological Society, but his abiding enthusiasm was for chemistry, thanks to his early friendship with Priestley, and he became the first Treasurer of the Chemical Society and its second President. So we started life with a close personal link between us.

However, the fledgling Society soon wanted to try its wings, and in six months it left the nest to go to the Westminster Literary and Scientific Institution in Leicester Square. There was some fear too that chemical experiments might not be welcomed in these august precincts. But migration was found to have its drawbacks; oddly enough there were difficulties about heating; they missed this warm nest, and in 1842 the Society was back in John Street, where it enjoyed the hospitality of the Society of Arts at the modest rent of £25 a year until 1849. The Annual Reports reveal the general satisfaction of the members with this arrangement, and indeed in 1844 the Council reported " that the arrangement . . . continues to be satisfactory to both parties, and especially to ourselves, as we have not only acquired a convenient habitation, but have avoided the expenses included in the word establishment so often ruinous to young Societies ". Happy indeed is the institution that has no overheads!

But by 1849, when the Society got its Charter, it had outgrown the limits of your kind hospitality, and needed rooms for its library and collections, which it found in the Strand. And so ended this happy connection between us, for which the Chemical Society will always be most grateful.

This year in July the Chemical Society is celebrating, somewhat belatedly, its centenary, and tonight we come here to commemorate its first meeting in the building where it took place. It is my privilege, in this joint meeting, to try and sketch the achievements not of the Chemical Society, for that is the task of the President, but the achievements of our science since 1841—what it has done, with the help of its sister sciences, to give man control over the materials on which his well-being depends, and to throw light on the complexities of living matter.

Chemistry in 1790—1840.

1841—just over half a century since Lavoisier had given chemistry its modern form in his great Treatise of 1789, his autobiography of one of the simplest and most decisive revolutions science has known. Lavoisier applied to chemistry not only the balance but, being skilled in affairs, the method of the balance sheet. The idea of the chemical equation dominated his mind, and his first chemical equation dealt, as the Bible tells us, with one of the earliest and one of the most significant chemical reactions known to man. It runs:

Le moût de raisin = acide carbonique + alkool.

We owe to Lavoisier the first clear distinction between physical and chemical change. With Laplace he laid the foundations of thermochemistry. We owe to him the idea of organic combustions by which he was the first to determine the quantitative composition of the products of living processes. When he was guillotined in 1794 he was setting his course towards the Atlantis of biochemistry.

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After Lavoisier in 1808 came Dalton with his Atomic Theory. It was one of those flashes of genius that crystallises an idea that had been floating in men's minds for centuries, and gives it the simple concrete form that makes it a powerful instrument in the hands of mankind. Lavoisier's analyses and his nomenclature could then be translated into atomic formulæ, the chemist's shorthand.

The next landmark was Davy's verification of Lavoisier's prediction of the existence of the alkali metals; their isolation by electrolysis laid the foundation of electrochemistry and of the association of chemical affinity with electrical charges. Davy also redressed the balance of Lavoisier's over-estimate of the central position of oxygen by showing that the essential element in an acid is hydrogen and not oxygen.

And then, just as chemistry was attracting more and more attention and new chemical facts were being discovered so rapidly, came the Swede, Berzelius—the most massive figure in the whole of its history. In a few years he determined single-handed with amazing skill and sagacity the atomic weight of every known element and the composition of many compounds, thus giving added reality to Dalton's theory. He too substituted for Dalton's geometrical symbols the initial letters of the names of the elements, which we use to-day. Berzelius had an encyclopædic mind, and he embodied in ten volumes the whole compass of chemical knowledge enriched by many of his own discoveries. Conservative as to the ideas which had served him well, he had the intuition to see where there was a common pattern in diverse chemical phenomena, and we owe to him the generalisations of isomerism and catalysis and their names.

For twenty years Berzelius was the accepted authority and the influence he exerted through his Annual Reports on current literature and through his friendships with the younger generation of chemists was immense. Meanwhile the younger men like Liebig, Wöhler, and Dumas were laying the foundations of organic chemistry by making series of derivatives from natural products with inorganic reagents. The new facts they discovered were difficult to reconcile both with the dualism and the theory of radicals which Berzelius had inherited from Lavoisier, and with his own view of the dependence of chemical affinity on electrically charged atoms. By 1841 his authority was seriously challenged. His formulæ were discredited, even his atomic weights were largely replaced by equivalents, and there was a drift from theory towards empiricism.

Founding of the Chemical Society.

So the Chemical Society was founded at a most opportune moment, when the number of young men doing research was rapidly increasing and the opportunity for discussion and publishing their results was badly needed. For the next twenty years chemistry was to be in a state of flux, without any generally accepted theory. It was a time of bitter controversy, when the older chemists resented criticism and the younger men like Gerhardt and Laurent suffered persecution for their views. In their heroic battle against authority, which they ultimately won, Pope's lines, often spoken in jest of our profession, came literally true:

> " The starving chemist in his golden views
> Supremely blest, the poet in his Muse ".

Laurent died as a result of privation.

From 1840 to 1860 the work of most outstanding chemists lay in organic chemistry. It was a period of rapid growth, when experiments were almost bound to lead to discoveries. Each chemist had his own theory of which he was tenacious, as it meant much to him; it was in a sense the scaffolding which enabled him to make his own contribution to the structure of chemistry. And so it is not surprising that by 1859 a whole page of Kekulé's text book was filled by the different formulæ proposed for such a simple substance as acetic acid.

As the technique of organic reactions was gradually developed, each year brought an increasing harvest of new compounds and there was a growing need for some new system of classification to include them all. Laurent and Gerhardt, with their logical French minds, had each been seeking a new basis of classification along rather different lines, and their partnership led eventually to Gerhardt's type theory in which all organic compounds were derived by substitution from four simple inorganic substances, hydrogen, water, hydrochloric acid, and ammonia. Gerhardt's theory was an unconscious recognition of the different combining powers of the atoms and groups, and led inevitably to Kekulé's theory of atom linkage. It had been a long struggle, and Laurent died in 1853, but Gerhardt lived until 1856 to taste success and see his views adopted by the younger chemists.

The early meetings of the Chemical Society during that stormy period must have been lively and stimulating, with men like Lyon Playfair, Graham, Brodie, William Odling

(Gerhardt's *l'ami Odling*), and Williamson, to whose classic paper on ether and alcohol Gerhardt owed so much. And there were in London during those years young German chemists of great ability—Kolbe came in 1845, to infect the young Frankland with his interest in the synthesis of organic compounds from simple molecules. Hofmann came in the same year to teach at the new College of Chemistry in Oxford Street, and Kekulé in 1853 as assistant to Stenhouse, the Chemist to the Mint. Kekulé often said that his theory of the structure of organic compounds started in his dream about atoms on the top of an omnibus one night between Islington and Clapham Road where he lodged. So in those days London and the meetings of the Chemical Society which took place in this building from 1841 to 1849 were a focus of chemical thought.

Cannizzaro and Kekulé.

These two decades of uncertainty and divided opinion ended almost abruptly after 1860, thanks to the constructive thinking of two men. In 1860 the first international conference of chemists was held at Karlsruhe at Kekulé's suggestion, with the object of arriving at some agreement about atomic weights and molecular formulæ. Nearly all the active workers in each country were present, but as at other international meetings progress was slow. Committees were appointed which grew larger and larger, there was jockeying for position and eventually the Congress broke up in a chilly mood, having accomplished practically nothing. But copies of a thin paper-covered pamphlet on atomic and molecular weights by Cannizzaro, the Professor of Chemistry at Palermo, were given to some of the delegates. His exposition of the existing difficulties and their solution by the consistent use of the laws of Avogadro and Dulong and Petit was so clear and convincing that as Lothar Meyer said when he read it " the scales fell from my eyes, doubts disappeared and were replaced by a feeling of certainty ". It was not long before there was a general agreement among chemists about the weights of the atoms and the number of atoms in a molecule, which, as Kekulé had foreseen, was a necessary preliminary to a general theory of the constitution of molecules.

The other decisive factor was Kekulé's theory of atomic linkages, each atom having a definite combining power—hydrogen one, oxygen two, nitrogen three, and carbon four. On this basis, recognising that atoms of carbon, unlike other elements, could unite to form stable chains, or rings like the six-membered benzene molecule, Kekulé was able to assign definite structures to organic compounds, and this gave an immense impulse to the advance of organic chemistry.

When these major controversies were over, chemistry advanced rapidly on a wide front in the years from 1860 to 1900 which form the next epoch.

Organic Chemistry, 1860—1900.

Kekulé's theory of atomic linkage had presented chemists with an almost unlimited number of possible arrangements of carbon atoms in straight or branched chains, or in rings with intermediate links of other atoms which could also form part of closed-ring structures. These possibilities chemists were quick to explore, both by building up new molecules by synthesis in the laboratory, and by trying first to ascertain the molecular structure of natural products and then to synthesise them in the laboratory. Outstanding examples of this were the syntheses of alizarin in 1869 and of indigo in 1880. In this way many new compounds were made and described, and the technique of organic reactions was continuously extended. Between 1856 and 1910 the number of known organic compounds increased from 3,000 to 200,000.

In this period of rapid development there was one episode of outstanding importance, the simultaneous recognition by van't Hoff and Le Bel of the need to take into account the arrangement of the atoms in three dimensions. Kekulé had realised this, but he was sceptical about the power of chemistry to reveal the actual structure of the molecule, although he thought physics might do so. Pasteur in 1845 had already proved from the rotation of light passing through them that in certain cases the same atoms could form either a right- or a left-handed molecule. Van't Hoff and Le Bel showed that this was due to the presence of one or more carbon atoms combined with four different groups which could be arranged spatially in right- and left-handed forms. In addition, the arrangement of the atoms in space could account for a number of other unexplained phenomena. All their predictions were quickly verified, and since 1874 stereochemistry, the arrangement of the atoms in space, has been a potent factor in the progress of organic chemistry.

During these years it was in Baeyer's laboratory that most of the foremost organic chemists served their apprenticeship. It was there that Emil Fischer, the younger Perkin, Willstätter, and many others learnt the simple technique of the test tube and glass rod with which so many

discoveries were made before the elaborate technique of modern organic chemistry became necessary. The sugars, the terpenes, and the alkaloids yielded the secrets of their structures. Some of the many new compounds that were synthesised were only of scientific interest, while others yielded new dyes or new perfumes or new drugs like eucaine and veronal, so called because Emil Fischer happened to wake up and look out of his carriage window at Verona after a visit to Baeyer to discuss its properties.

Inorganic Chemistry, 1860—1900.

The advance of inorganic chemistry naturally took a different course. In 1860 sixty-four elements were known and many attempts had been made to classify them in families with very limited success. When agreement had been reached as to the relative weight of the atoms a new line of attack was opened, and in 1864 both Newlands and Lothar Meyer pointed out that if the elements are arranged in the order of their atomic weights, elements recur at regular intervals with similar properties, apparently belonging to the same family. Four years later Mendeléeff, using more accurate atomic weights, developed the Periodic System in much greater detail and predicted by means of it the properties of three undiscovered elements which were missing from the system. The accuracy of his predictions was shown by the discovery of gallium in 1875, scandium in 1879, and germanium in 1886. The invention of the spectroscope by Bunsen and Kirchhoff in 1859 had given chemists a powerful new instrument, and the discovery of further new elements, rubidium, caesium, and thallium, soon followed with its aid, to fill other gaps in the Periodic Table of the elements. But even though it provided a basis for the classification of the elements in families, many puzzling problems in the Table remained unsolved.

Physical Chemistry, 1860—1900.

Meanwhile the influence of physics on chemistry was being felt more and more, both in the use of new techniques like the spectroscope and in various applications of physical theory. Here again van't Hoff was the pioneer in a dual attack by applying both molecular theory and the laws of energy to the analysis of chemical phenomena. The laws of energy or thermodynamics are laws of experience like Newton's law of motion, independent of any hypotheses as to the nature of matter, and affording therefore a useful test of the truth of such hypotheses and of classifying and forecasting certain chemical phenomena. Willard Gibbs had been the forerunner in this field in 1876—1878, but van't Hoff was the first to show the wide applications of thermodynamics to chemistry. At the same time he was analysing the kinetics of chemical reactions and the nature of chemical equilibrium in the light of molecular theory, and showed their dependence on the behaviour and properties of the individual molecule. Thus in the 'eighties a new subject, Physical Chemistry, was taking shape, especially in the field of solutions, where Arrhenius gave it a fresh impulse with his theory of electrolytic dissociation which related the electrical conductivity of solutions to the dissociation of molecules into electrically charged ions. That again had applications in many fields, and with the help of Ostwald and Nernst physical chemistry quickly became a powerful new instrument.

And so in the 'nineties, when I and my contemporaries were learning chemistry, organic chemistry gave us a tidy logical picture in which the agreement between properties and structure showed clearly that the model represented a close approximation to the truth. In physical chemistry we got a picture of the dependence of chemical reactions and equilibria on the kinetics of the individual molecule or ion, and of the value of thermodynamics in giving generalised laws independent of any theory. Inorganic chemistry was more difficult; by then there were so many isolated facts to be remembered, and while the Periodic Table was a great help, there were many anomalies still to be explained.

Nineteenth-century chemistry had been based on the Newtonian atoms, those small, hard, indivisible, elementary particles of which all matter was thought to be composed, and its development was mainly that of an experimental science. The whole picture of molecular constitution had been built up by inference from macroscopic experiments, and there were no means of investigating the fine structure of matter to give some clue as to the nature of the atoms, of their chemical affinity that caused their reactions, or of their valency that determined their combining powers. The evidence of their spectra certainly suggested that their structures were far from simple.

Then suddenly there came a rapid succession of discoveries that threw an entirely fresh light on the whole subject and by 1914 had given chemists a new conception of the unity and sub-mechanics of their science.

The Period of Great Discoveries, 1895—1913.

In 1897 J. J. Thomson discovered the negative electron, showing that electricity is atomic and that the electron is common to all atoms. Becquerel had already discovered radioactivity in 1896, and Madame Curie isolated radium in 1898. These discoveries, together with Rutherford and Soddy's systematic investigation of radioactive charges, gave the first clue to the nature of the atom.

Roentgen's discovery of *X*-rays in 1895, with wave-lengths approximating to atomic dimensions, in the hands of von Laue and the Braggs proved a most powerful means of investigating the arrangement of atoms and ions in crystals and later the arrangement of the atoms in the molecule.

In 1911 Rutherford's discovery of the dimensions and nature of the nucleus led to his theory of the nuclear atom consisting of a small central positively charged nucleus with electrons rotating in orbits around it. Moseley in 1913, by examining the frequencies of the *X*-rays emitted by different atoms, proved that there are ninety-two elements with ordinal numbers corresponding to the number of charges on the nucleus, thus throwing an entirely new light on the Periodic Table. As a proof of the thorough way in which nineteenth century chemists had done their work, it is worth noting that of that complex and hitherto mysterious group of elements, the rare earths, fourteen had been separated and recognised as elements before Moseley's law was known, leaving only one of extreme rarity to be found.

The full significance of Rayleigh and Ramsay's discovery in 1895 of argon, the first of the rare gases, followed by Ramsay's discovery of the rest of the family, was now apparent. The arrangement of the electrons in their atoms was so stable that they showed no tendency to combination, and this was the basis of G. N. Lewis's and Kossel's theories of valency as dependent on the stability of an octet of electrons in the outer shell of the atom.

In 1901 Planck had shown that radiant energy had a certain atomic character, as it could only be emitted and absorbed in discrete quanta, the size of which was proportional to the frequency of the vibrations. The fundamental significance of this discovery to chemistry was not at first obvious, until Bohr in 1912 showed that the application of the quantum theory to the electron orbits in Rutherford's atoms could explain the structure of their spectra, the actual wave-lengths of which could be calculated in simple cases.

Then, just as all the tools for future development were in the chemist's hands, came the war of 1914, the first chemists' war, in which chemistry played a vital part in making explosives, in making synthetic products to counter the effects of a blockade and in the military use of gas and smoke. The effect of this was to intensify the effort directed to chemical research after 1918.

Chemistry in the Inter-war Years.

Demobilised from their war activities, chemists returned to their laboratories with fresh zest to take up again the work that had held so many exciting prospects in 1914. I remember Rutherford saying to me in 1919: "What's the use of going back to chemistry when Bohr will soon to able to calculate anything you can find out?" But Rutherford was the last person to dissuade anyone from experimenting, and it was in his own laboratory that the science of nuclear physics was born.

During the inter-war years chemistry has progressed with amazing speed, and its influence has been felt increasingly in the sister sciences of physiology, botany, agriculture, and geology. The main factors in its progress have come from physics, both from new physical techniques and from new physical theories. Progress has been on such a wide front that it is impossible to summarise, but there seem to me four outstanding achievements in the fields of atomic and molecular structure, of nuclear physics and isotopes, of the kinetics of chemical action, and of the organic chemistry of living processes.

Atomic and Molecular Structure.

Chemistry owes to physics the detailed knowledge that we now possess of the structure of molecules, derived from measurements of their *X*-ray diffraction, electron diffraction, Raman spectra, dipole moments, and their spectra from the infra-red to the ultra-violet. There has been a continuous development both of the technique and of its application in each field since 1919. Thanks to this we now know the distances between the centres of the atoms in any linkage, the position of the atoms relative to one another, the nature of the linkage, the heat of formation of the linkage and its resistance to deformation.

Simultaneously with this advance on the experimental side there has been a remarkable

development on the theoretical side which has stimulated experiment and has explained the causes underlying the behaviour of the atoms and molecules.

Till 1925 the Bohr–Rutherford atom held the field, the positively charged nucleus with electrons rotating round it in various orbits. From the purely chemical side it gave a qualitative explanation of the valencies of the elements, it distinguished between electrovalent, covalent, and co-ordinate links, and it explained most of the regularities of the Periodic System. It gave a quantitative basis for calculating the spectra of atoms and simple molecules, and with the hypotheses of electron spin and molecular vibration it accounted for the fine structure of spectra and their behaviour in a magnetic field.

But difficulties arose with the model atom as the electron sometimes appeared to behave as a particle and at others as a wave motion, a dilemma that was the basis of Heisenberg's Uncertainty Principle. The difficulty was solved by the new calculus of quantum mechanics, in which the properties of the atom are described by equations which admit of no simple physical interpretation such as a model. The test of their validity is the wonderful accuracy with which they can predict the behaviour of single atoms. Unfortunately in more complex systems great mathematical difficulties are involved in a rigid solution, and various methods of approximation have to be adopted. However, in spite of this, quantum mechanics has provided a new stimulus and a new interpretation in many fields, particularly in regard to valency. It enables the direction of the valencies of any atom in space to be calculated, and provides a much more subtle differentiation of the various types of linkage. The periodicity of the properties of the elements with increasing atomic number can be shown to be a necessary consequence of the geometrical symmetry of the electron fields. It explains too the quantum restrictions as a necessary consequence of the wave characteristics of the electron.

Isotopes.

The nucleus itself is mainly the concern of pure physics, but there is one important exception, the existence of isotopes, atoms with the same atomic number but with nuclei of different mass. By means of his mass spectroscope Aston showed that the chemical elements are nearly all mixtures of istopes, and by measuring the amount of each present and its atomic weight he explained why chemical atomic weights are so far removed from whole numbers. The actual separation of the isotopes with identical chemical properties by physical means was one of the most laborious experimental problems with which chemists have been faced.

But a new significance was given to isotopes when the physicists found it possible by bombarding atomic nuclei with various particles to transmute them and often to produce isotopes with radioactive properties differing from those of the parent atom. Quite apart from their therapeutic importance, such isotopes could be used as tracer elements in chemical reactions and in living processes to track down the course followed by the atom in question.

Physicists also discovered the particles of which the nucleus is composed, the positron, the positive equivalent of the electron, and the neutron, whose unique properties as a projectile in nuclear bombardments makes possible the utilisation of atomic energy.

The Kinetics of Chemical Change.

This brings me to the next main field of progress, the kinetics of chemical reactions. It is generally true to say that no phenomenon is as simple as it seemed to the original discoverer, and of nothing is this so true as of the equations used to represent chemical reactions. Only last year our President's Bakerian Lecture was devoted wholly to the complexities of that first schoolboy equation: $2H_2 + O_2 = 2H_2O$.

The investigation of reaction rates has given scope for much ingenious experimental and mathematical treatment. It has involved the study of the lives of the individual molecules, the circumstances under which they can acquire a critical amount of energy, the effect of radiation, the effect of catalysts, and the significance of chain reactions. Great progress has been made, which has given us a much more intimate picture of the actual mechanism by which chemical reactions take place. The results are of profound interest for both theory and practice, as so often it is the rate of change that determines what is possible.

Organic Chemistry.

And lastly there is organic chemistry, when we must go back to where we left it about 1900. Its outstanding achievement has been the light it has thrown on the great systems of the materials and processes of living organisms. Organic chemistry has thus returned to the task for which

it was originally equipped by Lavoisier and for which he meant to use it, the discovery of the chemical reactions of the living body. Its success has been to reveal their complexity. With the techniques that have been developed by organic chemists for over a century they can now break down or build up the most complex structure of carbon atoms and the groups attached to them with a certainty that leaves no doubt as to what that structure is.

Here again physical methods have played an important part. *X*-Ray analysis of crystalline or regularly orientated material has revealed the details of its atomic and molecular structure. Infra-red spectra have made possible the identification of minute quantities of material differing only in small details of their structure. The modern methods of chromatography, the selective adsorption of substances in various media, allow of the separation of the constituents of complex mixtures available only in small quantities which otherwise could not be resolved. The ultra-centrifuge too has helped in the separation of complex molecules and the determination of their molecular weights. The technique of microchemistry, the handling and analysis of small quantities of organic material, has made possible the investigation of substances available only in small quantities and quickened the pace at which investigations can proceed.

The problem for the chemist, in conjunction with the physicist and the biologist, is to unravel the processes by which Nature builds up the structure of living organisms, and provides the materials that discharge the functions of their various parts.

The plant is the first stage in Nature's economy, as plants alone can assimilate the carbon dioxide of the air and nitrogen from inorganic sources and synthesise from them the carbohydrates, fats, and proteins that form the food of other organisms. The first success of chemists in this field was the determination of the structures of the simple plant products, such as the sugars, vegetable oils and fats, essential oils like the terpenes, rubber, alkaloids, and various dyestuffs and colouring matters like the anthocyanins. Many of these were synthesised in the laboratory, and *X*-ray analysis has confirmed the correctness of the structures assigned to them on the ground of chemical behaviour. A comparison of these structures shows that Nature makes use of the economy of prefabricated construction, as many of them are built up by different arrangements of the same groups of carbon atoms. Thus the carbohydrates are all built up of chains of six carbon atoms, but C_3 may be an intermediate stage in this grouping, as the groups $C_6 - C_3$ and $C_6 - C_3 - C_6$ frequently occur in plant products. The vegetable fats and oils are mostly built up of C_6 units forming chains containing twelve, eighteen, or thirty atoms, joined together by the C_3 of glycerin. The structural units C_6 and C_3 recur again in a number of substances where the chain of six carbon atoms has been converted into a ring as in the oil of cloves and similar substances. Two $C_6 - C_3$ groups provide the skeleton of many others, and with the addition of C_6 the skeletons of the catechins and anthocyanins. The aromatic oils, resins and rubber have been formed by a different route; they are built up from a C_5 unit with a branched carbon chain which may either condense to rings like the terpenes or polymerise to a long chain as in rubber.

But in spite of these regularities we have little knowledge of the methods by which Nature marshals these units in the living cell. Her catalytic methods are so specific in their actions and work so cleanly compared with ours that she is able to marshal these structural units to form complex molecules under the influence of surface forces exerted as it were by a template of existing molecules. The ease and certainty of Nature's methods is so intriguing and tantalising to the chemist working in a non-living environment.

It was quickly realised that many of the main constituents of living organisms, the polysaccharides and the proteins, had vastly greater molecules than these simple plant products, and here again *X*-rays have rendered decisive help. Cellulose, for instance, was found to consist of hundreds or thousands of glucose residues united in a straight chain, and forming the chain bundles which are the predominant structural element of the plant kingdom. In rubber the long carbon chains are folded higgledy-piggledy around one another, straightening when the rubber is stretched and giving it its elasticity. The discovery of formaldehyde phenol plastics by Baekeland in 1909 soon resulted in the synthesis of similar giant molecules in the laboratory and the study of their behaviour. Carother's classical investigation of the linkages which would produce these giant molecules led directly to the discovery of nylon, a nitrogenous synthetic fibre that is competitive with Nature's products.

Of all these giant molecules the proteins, which in one form or another enter into almost every living process, are the most significant. Emil Fischer's pioneer investigations showed that they all consist of various amino-acids linked together to form long chains. *X*-Ray analysis revealed the regular order in which the amino-acids alternate in the chains of different proteins and the position in space of the side groups, the projections from the chains that determine so

largely the specific properties of each. The proteins are divided into two great families, the fibrous and the globular, those in which the chains are extended like fibroin, the spider's web, and those in which they are coiled in a regular manner like albumin and hæmoglobin. The former class has again two main families, the keratin-myosin-fibrinogen group, including wool, hair, skin, nails, whalebone, muscle tissues, and the coagulating constituent of blood, and the collagen group including tendons, connective tissue, and cartilage. The knowledge of their chemical structure reveals something of the principles of Nature's engineering, of the way in which she provides for the necessary mechanical properties of the parts of an organism. And further it is beginning to throw light on the processes of growth, the synthesis of giant molecules by contact catalysis in living matter.

Great advances have been made in our knowledge of enzymes, those complex colloidal catalysts formed by living cells which enable the chemical changes that accompany and condition living processes to take place rapidly at ordinary temperatures. The isolation of some of them like urease, trypsin, and pepsin in a crystalline form was a great achievement. Some have proved to be pure proteins, while others, such as those responsible for the oxidation of food in the body, are proteins associated with various complex groups which can act as oxygen acceptors.

Then there are substances such as the vitamins, hormones, and auxins, small quantities of which exert such an immense effect on living functions. Vitamins are essential to normal life and healthy growth, and are all derived from foodstuffs. Their identification has played an important part in the modern treatment of nutrition, and the constitution of most of them is now known. Hormones are the chemical messengers, produced in one part of the body and exerting a most potent influence on others. Some of them, such as the sterols, and the active principles of others, such as adrenalin and thyroxin, have been isolated; their structures have been determined, and some of them have been synthesised. The knowledge gained in this way has been of the greatest value in curative medicine.

Lastly, there are the viruses, those minute carriers of disease that have been so hard to track down and isolate. Some of them have now been obtained in a crystalline form and have been shown to be nucleoproteins.

In addition to throwing light, in these and many other ways, on the complex molecules and the complex secrets of the chemical reactions on which the existence of life is dependent, chemists have synthesised many new substances which have important biological applications. Ehrlich's discovery of salvarsan in 1910 was an outstanding triumph. Its name "606" emphasises the number of attempts before a molecule was found that would destroy the spirochæte of syphilis without killing the patient. Later came the sulphonamides with their specific reactions against certain types of bacteria. Their power of stopping growth suggests that they are absorbed on the catalytic surfaces in place of some of Nature's prefabricated units of similar shape, and thus prevent the completion of the pattern and the formation of a new molecule. Their action has been likened to the jamming of a lock by a key that does not quite fit.

D.D.T. and gammexane come in another category. They are synthetic products of outstanding effectiveness in killing insect pests without hurting men or animals. Similarly a range of substances has been found which will kill weeds (dicotyledons) without damaging the growing crops which are monocotyledons.

One of the greatest triumphs of chemistry in the chemotherapeutic field has been the isolation of penicillin, and the elucidation of its structure, the last details of which were revealed by *X*-ray analysis, and finally its synthesis.

All these examples, and they are but a few of many, go to show what an effective instrument chemistry has become, working with her sister sciences in revealing both the possible combinations and permutations of the elements of which the world is made, and the nature of the processes associated with living organisms. But in addition, chemists have a great record of achievement in the application of all this accumulated knowledge to the service of mankind. And this brings me to the progress of chemical industry during the last hundred years.

Chemical Industry.

Our industry is, I know, of special interest to the Royal Society of Arts with its wonderful record of almost 200 years of activity devoted to the encouragement of the practical applications of scientific discovery. The progressive stages of civilisation have in fact been largely conditioned by the materials available to mankind. From the Bronze Age to the present age of

light alloys and plastics there has been a steady advance in the exploitation of natural materials to serve the needs of man, and in this the chemist has played the decisive rôle.

Chemical industry in 1841 was still in an embryo stage; it had not yet felt the effects of the great industrial expansion of the nineteenth century, or of the impact of science on industry. It was mainly concerned with the manufacture of acids, alkalis, and mineral salts, with the extraction of natural products like sugar and dyestuffs, and with various fermentation processes.

The first major development came from the progress of organic chemistry. Perkin's discovery in 1856 of mauve, the first synthetic dyestuff, started a new industry. One result was the first displacement of a natural product, when alizarin was synthesised in 1868, and the synthetic material quickly supplanted the cultivation of madder. Baeyer's synthesis of indigo in 1880 again led to the gradual displacement of the indigo crop.

With the rapid advance in the discovery of improved and faster colouring matters and the discovery of synthetic drugs like phenacetin and sulphonal, the organic industry grew rapidly. Although it had started in this country with Perkin, and Germans like Caro and Otto Witt came here to serve their apprenticeship, it was not long before Germany had secured the lead, mainly owing to her lavish investment in research. The scientific basis on which the organic industry had developed undoubtedly had a considerable influence on the development of the chemical industry as a whole.

In the heavy chemical industry the decisive episode in this country was I think the courageous and far-sighted decision of Ludwig Mond and John Brunner in 1872 to use the Solvay process for making soda. Their means were slender and several firms had already had to abandon the process. But Mond saw its possibilities, and for the first two years at Winnington he watched the process by day and night. The scientific control of the plant by which he achieved success and his skill in plant design marked the birth of chemical engineering in this country.

Other major factors were now at work to expand the scope of the industry. First came the demand for artificial fertilisers to meet the food demands of the rapidly growing industrial population. Then the availability of electrical energy from the dynamo gave a new impetus to the use of electrolytic methods to produce metals like aluminium, magnesium, and sodium, and alkali and chlorine, and of the electric furnace to make calcium carbide and other products.

The demand for explosives and the invention of gun cotton, dynamite, and high explosives built up another section of the industry. The peaceful uses of cellulose products—nitrocellulose, cellulose acetate, and viscose—provided another field of development, and in each new field the links between science and industry were drawn closer.

The successes of chemical engineering were achieved by plant design and process control. The design of plant was based on accurate quantitative knowledge of the reactions concerned, on securing maximum heat economy, on the use of an ever-increasing range of anti-corrosive materials, and on the use of the most efficient catalysts. Continuous control of processes was obtained by recording instruments at each stage and by analysis. The study of catalysis led to revolutionary changes first in the manufacture of sulphuric and nitric acids and ammonia and later in the whole range of the industry. The catalytic hydrogenation of vegetable oils was an outstanding contribution towards the supply of the world's demand for fats.

Then came the war of 1914, in which the chemical industry became almost a decisive factor by the production of explosives and fertilisers. In fact, without the Haber process for making ammonia, the blockade would quickly have compelled Germany's surrender. The war thus demonstrated the strategic importance of the chemical industry. To quote a sentence from the report of the Mission which I had the privilege of leading in 1919 to investigate the war uses of the German chemical factories: "In the future it is clear that every chemical factory must be regarded as a potential arsenal, and other nations cannot, therefore, submit to the domination of certain sections of chemical industry which Germany exercised before the war. For military security it is essential that each country should have its chemical industry firmly established". The lesson we learnt then was not forgotten.

As in pure chemistry, the inter-war period was a time of rapid development. The earlier development of synthetic chemistry had largely been in competition with Nature. Steinmetz, the genius of Schenectady, once said to the head of the I.G., "Bosch, I know you can make indigo cheaper than God, you may some day make rubber cheaper than God, but you will never make cellulose cheaper than God".

With the discovery of plastics and the vast possibilities of the synthesis of large molecules there has been some competition with natural products, such as nylon with silk, and synthetic rubber with the plantation product, but much progress has also been made in processing and

upgrading vegetable products, such as cellulose, starch, and vegetable oils, and in the use of farm by-products. The processing of foodstuffs, including crop drying, is another field in which chemical industry and agriculture are establishing a new community of interest. These developments are of great significance, as it means that industry is drawing increasingly on the revenue account instead of the capital account of the world's resources for its raw materials.

I must not omit, however, some reference to the remarkable technical progress of the petroleum industry in the inter-war years. The refining of crude oil was revolutionised by the use of catalysts, and most recently by the use of the so-called fluid catalyst, small particles suspended in a current of the reacting gases. In addition to making petrol of high octane value and other fuels, a new industry has been built up on the hydrocarbon gases from the cracking process and the natural gas from the oilfields. From them an immense variety of chemicals are now made, such as *iso*octane, synthetic rubber, and solvents of all kinds. Under the pressure of autarchy oil was made from coal, by hydrogenation and by the Fischer–Tropsch process, which is now expected to produce petrol and hydrocarbon gases at a price competitive with crude oil, starting from natural gas and using a fluid catalyst.

Once again we have seen how war has tested the resources of the chemical industry, when it proved its ability to produce, at a cost, whatever was needed from the available raw materials, whether it was aviation fuel, rocket fuel, synthetic rubber, or synthetic fibres. Chemical engineers too played a great part in the vast organisation, with all its attendant difficulties, necessary to separate the quantities of uranium 235 and plutonium in the state of purity needed for the atomic bomb. And their work opens up a vista of possibilities of the use of atomic energy for peaceful purposes.

Conclusion.

Thus in its industry, as in pure science, chemistry has a great record of achievement. Looking back at the state of knowledge when our Society was founded here in 1841, we see a wonderful century of progress. And in this the Fellows of the Society have always played a leading part. But it is well to remember that that swift advance has depended on the efforts of men in many countries working together with a common aim, with no tariffs or visas to hinder the flow of new ideas.

And I cannot help reflecting on the contrast between this record of achievement and the sorry state of the world to-day. Is it not paradoxical that with the understanding we have won of Nature's secrets, with our power to control nature in action, that the majority of mankind should still be suffering from malnutrition and many from endemic disease? This seems to me a challenge to science and not least to chemists. Is sufficient effort being devoted to the application of the knowledge we already possess? What should be the priorities? How can we ensure that the same concerted effort is made to use that knowledge for the peace and contentment of the world as made it such a potent factor in the war? That is the thought I would leave with you at the beginning of our second century.

The Development of Electrochemical Theories of the Course of Reactions of Carbon Compounds.

THE EIGHTEENTH FARADAY LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY ON JULY 16TH, 1947.

By SIR ROBERT ROBINSON, M.A., D.Sc., LL.D., P.R.S.

THERE are many tributaries to the river of scientific progress, and their contribution to the broad stream persists in spite of inevitable loss of individual form.

So, the modern theories of molecular structure and chemical reactions which flourish in the domain of physical chemistry, thermodynamics, and wave mechanics, are derived from many sources. It is my intention to speak of only one of these, namely that provided by the generalisations of their experience which organic chemists have been able to make in terms of the electronic conception of valency.

That these generalisations were a real forward step cannot be doubted, but the form in which they were expressed has naturally been altered in accordance with the successive advances in our knowledge of the fundamentals of chemical kinetics and atomic and molecular theory.

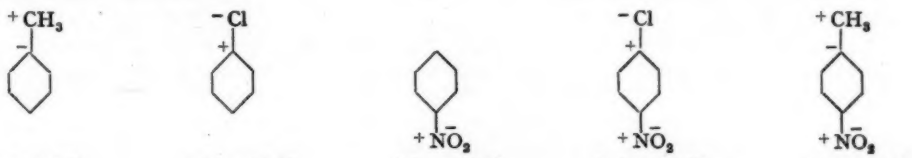
The identity of the ideas has not yet been lost, however, and the qualitative approach still affords a valuable framework for the elaboration of detail by means of the more searching methods of analysis which are now available. But the section of the subject that I have indicated is small only in relation to the whole; it is very complex in itself and is the outcome of developments in varied fields of work. It will be convenient to follow the thread suggested by the lecturer's contacts with the topic and by precedent and parallel investigations, but it is certain that, by a change of emphasis, many different lectures could be delivered under the same title.

After the discovery of the electron by Sir Joseph Thomson and the successive stages in the formulation of the electrical theory of the constitution of matter, the conceptions of the nature of chemical affinity and valency bonds were gradually adjusted, and attempts were made to explain the chemical properties of molecules as assemblages of electrons and positively charged nuclei. Some kind of electronic theory of valency became almost axiomatic, but, as the development showed, there was ample scope for divergent views of details of structure, of the nature of the forces involved, and of the interpretation of physical and chemical properties. The idea of covalency, the sharing of electrons by two nuclei, was adumbrated by Ramsay in 1908. Thomson and Stark developed more detailed theories, and were among the first to attack problems of organic chemistry on an electronic basis.

The speculative elaborations of Stark ("Die Elektrizität im chemischen Atom", Leipzig, 1915), who also advanced electronic explanations of optical properties, have not survived in their original form. Many of his suggestions may, however, be traced in later theories. A second epoch may be roughly defined as that of Kossel (*Z. Physik*, 1920, **1**, 395) and of Lewis (*J. Amer. Chem. Soc.*, 1916, **38**, 762; "Valence and the Structure of Atoms and Molecules", Amer. Chem. Monograph, 1923), characterised, at least in its earlier phases, by somewhat rigid conventions in regard to the chemical bond, and by great advances in our knowledge of the relation of structure to physical properties. In the third and present period the applications of wave mechanics are yielding more precise information in regard to the distribution of electrons in the molecules. In certain cases that distribution can even be determined from experimental observations of the reflexion of *X*-rays by crystals. These matters lie outside the purview of the present lecture. Indeed, the symbols which we still employ are largely independent of stereo-electronic considerations. The exceptions are those used for the polar molecules, to the study of which Debye has made such outstanding contributions, and for the ions, that is to say the bound and free ions. At every stage of the electrochemical theory these are our trusted guides.

Langmuir pointed out that trimethylamine oxide, formed from electrically neutral NMe_3 and an uncharged oxygen atom, must be $Me_3\overset{+}{N}—\overset{-}{O}$ by the arithmetic of the electrons, and Sidgwick extended the idea to include many compounds containing the co-ordinate link $A \overset{(+)}{\longrightarrow} \overset{(-)}{B}$ ("The Electronic Theory of Valency," Oxford, 1927). The existence of these dipolar groups has been fully established by experiment and has been correlated with a range of physical and chemical properties. The knowledge has been used to confirm the assumed orientation

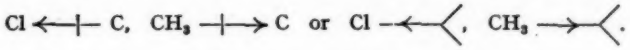
of electrostatic doublets produced by simple substitutions. For example, on theoretical grounds Thomson showed that such a doublet should be present in the group C–Cl, and this is confirmed by the fact that methyl chloride has an electric moment, $1{\cdot}97 \times 10^{-18}$ e.s.u., in the gaseous state. The direction of the moment is shown by a comparison of the dipole moments (e.s.u.) of chlorobenzene, nitrobenzene, and *p*-chloronitrobenzene, because NO_2, a dipole like an amine oxide, must be $\overset{+}{N}\overset{-}{O}_2$.



$0{\cdot}4 \times 10^{-18}$ $1{\cdot}5 \times 10^{-18}$ $3{\cdot}9 \times 10^{-18}$ $2{\cdot}6 \times 10^{-18}$ $4{\cdot}5 \times 10^{-18}$

(All in benzene solution.)

It is clear that the separate dipole moments due to C–Cl and C–NO_2 are in opposite directions in the molecule, or in other words they are in the same direction with respect to the nucleus. Substitution of methyl for hydrogen in the aromatic nucleus produces a small dipole moment in the opposite sense. We denote these displacements by the symbols:



Both Thomson and Lewis assumed that such doublets would exert an effective field, either directly or by induction through a chain of atoms, and gave in illustration the greater strength of the chloroacetic acids as compared with acetic acid. The operation of the electrical field on the carboxyl group will obviously enhance the stability of the anion produced by electrolytic dissociation. As expressed by Lowry the sheath of electrons moves towards the chlorine atom and thus bares the nuclei of the oxygen atoms, enhancing their repulsion on the attached proton.

Lewis pointed out that the effect diminishes as the chlorine atom is removed from the carboxyl. Thus α-chloropropionic acid is about as strong as chloroacetic acid, but β-chloropropionic acid is much weaker. γ-Chlorobutyric acid is still weaker, and the effect is hardly discernible in δ-chlorovaleric acid.

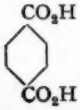
Ionisation constants of aliphatic acids.

		K.
	$CH_3{\cdot}CO_2H$	$2{\cdot}1 \times 10^{-5}$
(Br)	$CH_2Cl{\cdot}CO_2H$	$1{\cdot}55 \times 10^{-3}$ (Br, $1{\cdot}38 \times 10^{-3}$)
	$CHCl_2{\cdot}CO_2H$	5×10^{-2}
	$CCl_3{\cdot}CO_2H$	2×10^{-1} (?)
	$CH_3{\cdot}CH_2{\cdot}CO_2H$	$1{\cdot}4 \times 10^{-5}$
(Br)	$CH_3{\cdot}CHCl{\cdot}CO_2H$	$1{\cdot}47 \times 10^{-3}$ (Br, $1{\cdot}08 \times 10^{-3}$)
(Br)	$CH_2Cl{\cdot}CH_2{\cdot}CO_2H$	$8{\cdot}59 \times 10^{-5}$ (Br, $9{\cdot}8 \times 10^{-5}$)
	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	$1{\cdot}6 \times 10^{-5}$
(Br)	$CH_3{\cdot}CH_2{\cdot}CHCl{\cdot}CO_2H$	$1{\cdot}39 \times 10^{-3}$ (Br, $1{\cdot}06 \times 10^{-3}$)
	$CH_3{\cdot}CHCl{\cdot}CH_2{\cdot}CO_2H$	$8{\cdot}94 \times 10^{-5}$
(Br)	$CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	3×10^{-5} (Br, $2{\cdot}6 \times 10^{-5}$)
	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	$1{\cdot}5 - 1{\cdot}6 \times 10^{-5}$
(Br)	$CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	$2{\cdot}04 \times 10^{-5}$ (Br, $1{\cdot}9 \times 10^{-5}$)
	$CH(CH_3)_2{\cdot}CO_2H$	$1{\cdot}5 \times 10^{-5}$
	$C(CH_3)_3{\cdot}CO_2H$	$9{\cdot}8 \times 10^{-6}$
	$CH_3{\cdot}[CH_2]_4{\cdot}CO_2H$	$1{\cdot}45 \times 10^{-5}$
	$CH_3{\cdot}[CH_2]_5{\cdot}CO_2H$	$1{\cdot}46 \times 10^{-5}$
	$CH_3{\cdot}[CH_2]_6{\cdot}CO_2H$	$1{\cdot}44 \times 10^{-5}$
	$CH_3{\cdot}[CH_2]_7{\cdot}CO_2H$	$1{\cdot}44 \times 10^{-5}$

Dippy and R. H. Lewis (*J.*, 1937, 1008) noted an almost linear relation between the dipole moments and the electrolytic dissociation constants of a number of acids.

In the series of the dibasic acids we can study the effect of one carboxyl on the strength of another at varying distances.

Ionisation constants of dibasic acids.

	K_1.	K_2.
$CO_2H \cdot CO_2H$	7×10^{-2}	$3–7 \times 10^{-5}$
$CO_2H \cdot CH_2 \cdot CO_2H$	$1{\cdot}46—1{\cdot}63 \times 10^{-3}$	$2{\cdot}1(1{\cdot}4) \times 10^{-6}$
$CO_2H \cdot CH_2 \cdot CH_2 \cdot CO_2H$	$8{\cdot}1 \times 10^{-5}$	$3{\cdot}7 \times 10^{-6}$
$CO_2H \cdot [CH_2]_3 \cdot CO_2H$	$4{\cdot}7(6{\cdot}9) \times 10^{-5}$	$2{\cdot}9 \times 10^{-6}$
$CO_2H \cdot [CH_2]_4 \cdot CO_2H$	$3{\cdot}7 \times 10^{-5}$	$2{\cdot}4 \times 10^{-6}$
$CO_2H \cdot [CH_2]_5 \cdot CO_2H$	$3{\cdot}23 \times 10^{-5}$	$4{\cdot}4 \times 10^{-6}$
$CO_2H \cdot [CH_2]_7 \cdot CO_2H$	$2{\cdot}5 \times 10^{-5}$	$2{\cdot}4 \times 10^{-6}$
$CO_2H \cdot [CH_2]_8 \cdot CO_2H$	$2{\cdot}7 \times 10^{-5}$	$2{\cdot}5 \times 10^{-6}$
	$1{\cdot}3 \times 10^{-3}$	$3{\cdot}4—5{\cdot}8 \times 10^{-6}$
	$2{\cdot}9 \times 10^{-4}$	$2{\cdot}4 \times 10^{-5}$
	$1{\cdot}5 \times 10^{-4}$	
$Ph \cdot CO_2H$	$6{\cdot}5 \times 10^{-5}$	

It is apparent that $\cdot CO_2H$ behaves like C—Cl. As Thomson's electrostatic argument suggests,* it must be represented as $\overset{\delta+}{-}\overset{\delta-}{C}\ O_2H$, and it is electron-attracting. But after dissociation the group becomes $-\overset{-}{C}O_2$; there is now no question of a dipole,† but only of a negative charge which should repel electrons and conversely hold protons even at a distant point. The second dissociation constants clearly show that this anticipated reversal of the effect occurs.

The values quoted for K_2 are not always strictly comparable with one another, or with those for K_1. The second dissociation constants were in some cases determined at 100° by the method of inversion of sucrose (cf. Smith, *Z. physikal. Chem.*, 1898, **25**, 220). It may be noted that E. Q. Adams (*J. Amer. Chem. Soc.*, 1916, **38**, 1503) has shown that if the first dissociation had no effect on the second, K_2 should be one-fourth of K_1. When the carboxyl groups are far removed from one another, this relation was found to hold approximately (cf. Chandler, *J. Amer. Chem. Soc.*, 1908, **30**, 694).

The case of isomeric acids differing in stereochemical configuration is particularly convincing.

Ionisation constants of stereoisomeric dibasic acids.

	K_1.	K_2.
$\begin{matrix} CH \cdot CO_2H \\ \| \\ CO_2H \cdot CH \end{matrix}$	$9{\cdot}8 \times 10^{-4}$	$2{\cdot}7 \times 10^{-5}$
$\begin{matrix} CH \cdot CO_2H \\ \| \\ CH \cdot CO_2H \end{matrix}$	$1{\cdot}3 \times 10^{-2}$	$2(2{\cdot}6) \times 10^{-7}$
$\begin{matrix} CMe \cdot CO_2H \\ \| \\ CO_2H \cdot CH \end{matrix}$	$8{\cdot}5 \times 10^{-4}$	9×10^{-6}
$\begin{matrix} CMe \cdot CO_2H \\ \| \\ CH \cdot CO_2H \end{matrix}$	$3{\cdot}8 \times 10^{-3}$	$2{\cdot}4 \times 10^{-7}$ (100°)

The *cis*-acids are much the stronger as monobasic acids but they are far weaker in the second ionisation step. The ratio of K_1 to K_2 for fumaric acid is about 36 and for maleic

* However, in opening a discussion on these topics in 1923 (Faraday Society) Sir Joseph Thomson classed Cl, OH, NH_2, and CH_3 together ($\overset{+}{C}—\overset{-}{Cl}$) and distinguished their effect from that of CN and NO_2 ($\overset{-}{C}—\overset{+}{C}N$). This view appears to have been based on some kind of alternation and disregards the inductive transmission of the field of a doublet. Thus $\overset{+}{C}\overset{-}{N}$ distributes a positive field over the atoms to which it is attached and, of the groups mentioned, $\overset{-}{C}H_3$ is the only one that produces a negative field.

† This is not true of the sulphonic ion, SO_3^-. Thus K_2 for *p*-sulphobenzoic acid is $1{\cdot}4 \times 10^{-4}$ ($>K$ for $Ph \cdot CO_2H$, $6{\cdot}5 \times 10^{-5}$). There is other evidence that SO_3^- distributes a *positive* electric field over an attached group, and this is clearly due to its constitution $—S^{++}O_3^{-\,-\,-}$, the nearer double positive charge being more effective than the more remote triple negative charge.

acid about 50,000. Attention should be paid to the order of the phenomena only, as, apart from the experimental difficulties, the interpretation is complicated by the possibility of differences of solvation of the acids and their ions.

Many of these facts were established by the work of Walker, Ostwald, and Bone, Sprankling, and Sudborough fifty to sixty years ago, and Ostwald gave the acceptable explanation of them in general terms (*Z. physikal. Chem.*, 1889, **3**, 177).

The whole problem of the strengths of acids and bases (where the effects are naturally reversed) can be satisfactorily treated along similar lines, but, as Flürscheim was the first to show (*J.*, 1909, **95**, 718; 1910, **97**, 84), steric hindrance must be taken into account in many cases, for example in *o*-substituted benzene derivatives. We may regard the dissociation constant of a carboxylic acid as a measure of the electrical field over the dissociating group, provided that approach of solvent molecules is not hindered by steric conditions.

I have dwelt at some length on this clear case because of its historical importance and in order to place in juxtaposition with it, experimental results from which it can be seen that exactly analogous phenomena control the nitration of certain benzene derivatives in the *o*-, *p*-, or *m*-positions with respect to a substituent. With the acids we have an ionic equilibrium and the effect of an electric field is not surprising. But in the nitration case we have an effectively irreversible process and no obviously ionic reaction.

The work of Vorländer showed that the direct attachment of an 'onium group to the benzene nucleus gives substances that nitrate exclusively in the *m*-position (*Ber.*, 1919, **52**, 262, 274; Vorländer and Siebert, *ibid.*, p. 283). This may be compared with the *m*-nitration of nitrobenzene (benzoic acid, benzenesulphonic acid, etc.):

The "'onium" atom need not be nitrogen but may be sulphur, selenium, phosphorus, arsenic, antimony, bismuth, lead, or even iodine [Vorländer and Büchner, *Ber.*, 1925, **58**, 1898 (I); Vorländer and Schroedter, *ibid.*, p. 1900 (Bi, Pb); Michaelis and Soden, *Annalen*, 1885, **229**, 324 (a P compound not quite analogous); Ingold, Shaw, and Wilson, *J.*, 1928, 1280 (P, As, Sb); Baker and Moffitt, *J.*, 1930, 1722 (S, Se)].

The interpretation given by Vorländer laid emphasis on the direct union of the "'onium" atom to the nucleus and is no longer considered valid.

In 1902 Schultz and Bosch (*Ber.*, 1902, **35**, 1292) stated that phenylbenzylethylamine nitrated in the *m*-position in the benzyl group, and Noelting and Kregeczy (*Bull. Soc. chim.*, 1916, **19**, 355) recorded the *m*-nitration of benzyldiethylamine, both in strongly acid solution. The significance of these isolated observations was not quickly recognised, mainly because there was no orientation theory that was generally considered satisfactory. A few years later interest was wakened and an active discussion arose in this country on the question of the actual substance that nitrates in the *m*-position. Was it the base or the salt? This was settled in favour of the latter view by Ing and the lecturer (*J.*, 1926, 1655) who found that benzyltrimethylammonium nitrate furnished nearly 90% of the *m*-nitro-derivative. In this quaternary salt the existence of free base is naturally impossible. The paper was entitled "The orienting influence of free and bound ionic charges", and the *m*-nitration in this and other cases was attributed to an electrical field produced by the cation over the molecule. The result was of great importance because it demonstrated that the charged centre need not be directly connected to the nucleus.

In a footnote it was stated that the work would be extended to β-phenylethyltrimethylammonium nitrate and γ-phenylpropyltrimethylammonium nitrate in order to determine the influence of the length of chain separating the charged centre and the nucleus. Even in the former case the nitration was chiefly in the *p*-position. Quantitative details of these and other examples were later provided by the extensive work of Ingold and his school.

It was found that, when a cationic charge is separated by a methylene group from the benzene ring, the nature of the 'onium atom is significant. Other things being equal the heavier atoms are the less effective, possibly because the distance from the aromatic nucleus is increased by their larger radius and the nuclear positive charge is more diffuse. Examination of the results demonstrates conclusively that the proportion of *m*-nitration is dependent on the intensity of the positive electric field over the nucleus.

m-*Nitration of 'Onium Salts*, Ph·R.

R = CH_2·NMe_3^+, 88;[1] R = CH_2·CH_2·NMe_3^+, 19%;[2] R = CH_2·CH_2·CH_2·NMe_3^+, about 5%;[3] R = PMe_3^+, 100%;[4] R = CH_2·PMe_3^+, 10%;[4] R = $AsMe_3^+$, 98%;[4] R = CH_2·$AsMe_3^+$, 3·4%;[4] R = $SbMe_3$, 86%;[4] R = SMe_2^+, 100%;[5] R = CH_2·SMe_2^+, 52%;[5] 2-phenylbenzopyrylium salts[6] and 2-phenylquinoline metho-salts,[7] only *m*-nitro-derivatives were isolated, and in high yield.

[1] Ing and Robinson, *loc. cit.*; Goss, Ingold, and Wilson, *J.*, 1926, 2240. [2] Goss, Hanhart, and Ingold, *J.*, 1927, 250. [3] Ingold and Wilson, *J.*, 1927, 810. [4] Goss, Ingold, and Wilson, *loc. cit.* [5] Baker and Moffit, *loc. cit.*; Pollard and Robinson, *J.*, 1930, 1765, found Ph·CH_2·SEt_2^+, *m*-nitration, 28%. This fall, as compared with the benzyldimethylsulphonium salt, is probably due to reduction of the positive 'onium field of sulphur by a negative field due to the methyl groups. [6] Le Fèvre, *J.*, 1929, 2771. [7] Le Fèvre, *J.*, 1930, 2236.

Flürscheim and Holmes (*J.*, 1926, 1562) and Pollard and Robinson (*J.*, 1927, 2770) found cases in which the electrostriction of the cations by added salts diminished the percentage of *m*-nitration. Thus benzyldiethylamine in an excess of sulphuric acid gives 53·5% of the *m*-derivative. When ammonium sulphate was added the proportion fell to the region of 33%. The nitration of benzylpiperidine in nitric acid (*d* 1·5) gives about 70% of the *m*-nitro-base, and addition of trimethylammonium nitrate or rubidium nitrate, salts which are soluble in nitric acid, caused progressive reduction as more of the salts was added, until only about 20% of the *m*-derivative was produced. It was suggested that the accessibility of, for example, a sulphonium cation to electrostriction may be a part of the cause of the less intense field (as compared with a corresponding ammonium cation) that it exerts over the aromatic nucleus.

It was pointed out long ago by Holleman ("Die direkte Einführung von Substituenten in den Benzolkern", 1910, p. 469) that predominant *op*-substitution occurs at a higher rate and under milder conditions than predominant *m*-substitution.

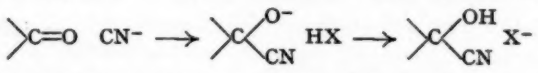
This is easy to understand in the series which has been discussed because the recent work of Bennett and Ingold and their collaborators has indicated that the effective nitrating agent, at least in sulphuric acid solution, is the nitroxyl ion, NO_2^+. Obviously this will be repelled by a positive field and will enter the molecule the more easily the less intense the field. The relation indicated by this example is general and is often diagnostic of an ionic type of reaction. In regard to the actual rates in different cases Wibaut (*Rec. Trav. chim.*, 1915, **34**, 241) found the order C_6H_5·$CH_3 > C_6H_6 > C_6H_5Cl > C_6H_5Br$ in acetic anhydride solution. Using the method of competitive nitration, Ingold and Shaw (*J.*, 1927, 2918) calculated from their results that each *o*- and *p*-position in toluene is roughly thirty times as reactive as in benzene, and each *m*-position about twice as active as one of the positions in benzene. The ratio $R_{C_6H_5R}/R_{C_6H_6}$ was found to be R = I, > 1; R = Br, 0·2; R = Cl, 0·01; R = F, 0·002. Ingold, Lapworth, Rothstein, and Ward (*J.*, 1931, 1959) working under somewhat different conditions increased the figures for toluene and found that one of the *m*-positions is about three times as active as one position in benzene. Although the assumptions made in the calculations hold only approximately and may be arguable, the general trend of the phenomena was established. It is in agreement with the theory outlined that the *m*-position of toluene should be activated (see below).

Excluding the cases (conjugated systems) considered later, all the data on benzene substitution can be shown to be in harmony with these principles. If we withdraw electrons from the nucleus as by substitution of halogens, nitro-groups, carboxyl groups, etc., for hydrogen in the side-chain we augment *m*-nitration. Introduction of methyl groups into the side-chain augments *op*-nitrations. Nitration has been studied very extensively but enough is known of sulphonation and halogenation to demonstrate that the orientation in these processes follows the same general lines. In order to be able to discuss why *m*-nitration occurs under the influence of a positive electric field, it is necessary to study other aspects—the reagents, and the behaviour of unsaturated systems.

The Classification of Reagents as Anionoid and Cationoid.—These terms introduced by Lapworth (*Manchester Phil. Soc.*, 1925; cf. *Nature*, 1925, **115**, 625) implied that certain electrically neutral molecules exhibit reactions of ionic type. Thus the hydroxyl ion combines with a proton to form water, and when water combines with a proton to form the solvated hydrogen ion, the process is evidently analogous. Hence the water molecule is said to be anionoid or to be an anionoid complex. The terms are equivalent to electron-donor and electron-acceptor and also to Ingold's expressions nucleophilic and electrophilic, respectively.

When a neutral molecule is attacked by an ion, the site of a cationoid or anionoid position is easily located, and it was just such a case that led Lapworth to develop his system of incipient

alternate polarities. The reference is to the formation of cyanohydrins which were conclusively demonstrated, qualitatively and by kinetic studies, to result from the attack of cyanidion on a carbonyl group. The resulting complex ion then takes a proton from a suitable source, such as water or an alcohol, or even from a molecule of hydrocyanic acid:

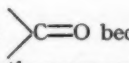
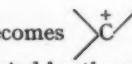
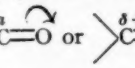
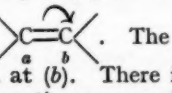


Thus pure hydrocyanic acid does not combine with aldehydes or ketones, but the alkali from a glass vessel is sufficient to start the succession of processes.

Hence the carbon of the carbonyl group is said to be " cationoid ". All the characteristic reactions of carbonyl compounds conform to this view. By analogy we also class many similar groups as cationoid, for they evidently undergo the same type of reactions. These include carboxyl and especially the carboxylic ester group, the cyano- of nitriles, nitrosyl and nitroxyl groups.

The cationoid character of the carbon of $-CO-$ could be deduced theoretically from the fact that oxygen has a greater affinity for the negative charge than carbon, but there is no such guide in the case of the carbon–carbon double bond, and a conclusion had to be based on what was already known of the characteristic behaviour of olefins. This knowledge was sufficient for the purpose but it was eked out by specifically designed tests, among which may be mentioned Gilman's demonstration that olefins are inert towards organometallic compounds.

Consideration of the reactions of the olefins showed that in general and under ordinary conditions, they are easily attacked by cations and cationoid reagents but are relatively inert to anions and anionoid reagents. They were therefore regarded as anionoid. But this only means that their additive reactions are *usually initiated* by electron-donation to reagents; there must always be a subsequent process in the course of which the second carbon of the system evinces cationoid character.

In the formation of cyanohydrins it is clear that the group  becomes  , and any part of this full displacement of an electron pair is conveniently represented by the symbols or  . Similarly any part of the full displacement of a pair of electrons in an olefin can be represented as  . The difference is that whereas the carbonyl is cationoid at (*a*) the olefin is anionoid at (*b*). There is complete analogy between the reactions of the olefins and those of the aromatic compounds which tend to retain their type, and therefore benzene, and all similar substances, are also classed as anionoid.

Saturated carbon, midway between lithium and fluorine, has little or no intrinsic tendency to be either anionoid or cationoid. Therefore alkyl groups exhibit either behaviour in accordance with the electrochemical character of the group or atom to which they are united. Thus a chlorine atom holds the covalency electrons tenaciously and tends to separate as an ion. An attached alkyl group is consequently cationoid. But metals easily relinquish electrons and hence the alkyls of organometallic compounds are anionoid.

R(—Cl R—)MgX

The annexed table requires little further explanation and can, of course, be greatly extended.

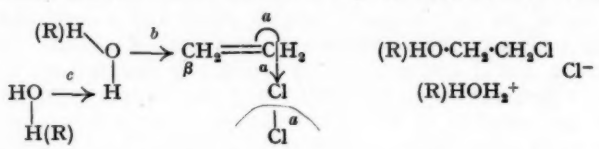
Anionoid.	Cationoid.
Nucleophilic.	*Electrophilic.*
Electron-donating.	*Electron-accepting.*
Active anions (OH^-, CN^-, etc.).	Active cations (H_3^+O, ϕN_2^+).
Anionoid complexes with unshared electrons (R_3N, ROH, etc.).	Atoms with incomplete electron configurations (neutral O; Co, Pt, etc.; BF_3, $AlCl_3$).
Reducing agents ($Fe^{++} \longrightarrow Fe^{+++}$).	Oxidizing agents $[Fe(CN)_6^{----} \longrightarrow Fe(CN)_6^{---}]$.
Metals as electron sources.	Halogens, nitric acid (in nitration), sulphuric acid (in sulphonations).
R in R_2Zn, RMgX, etc.	R in RCl, R_2SO_4, $\vdots NR^+$, etc.
$:C=C:$, C_6H_6, etc.	$:C=O$ (at carbon), etc.
Free radicals.	Free radicals.

In all the classes the various representatives can be arranged in order of reactivity, and one general principle is that unshared electrons are better donors, the smaller their number.

This is connected with a closer approximation to the rare gas configuration. A negative charge on the reagent molecule naturally enhances the ease of electron donation, but even a positive charge need not entirely suppress the process. Conversely a positive charge enhances the activity of an electron acceptor, an example being the catalysis of carbonyl reactions by acids, due to the complex $:C{=}\overset{\curvearrowright}{O}H^{+}$. And again a negative charge does not always inhibit carbonyl activity completely. It was only gradually realised that the potentiality for covalency transformations is given by unshared electrons, or electrons in defect of a normal configuration, and that the charges either help or hinder the reactions.

The symbols suggested for electron displacements, together with Sidgwick's for the co-ordinate link, can conveniently be used to illustrate the course of reactions and one example will suffice. This is the formation of glycol chlorohydrin (or an ether, R·O·CH_2·CH_2Cl) from ethylene, chlorine, and water (or an alcohol, R·OH).

The lecturer (Institut International de Chimie Solvay, Quatrième Conseil, Brussels, 1931; Gauthier-Villars, Paris, 1931, p. 460. The use of R·OH as well as H_2O was mentioned in subsequent lectures and was known to Professor Noyes) suggested the following cycle:



(*a*) The anionoid ethylene donates electrons from C_α to cationoid chlorine, from which a chloridion is gradually produced.

(*b*) When the process of electron depletion of C_β has reached a certain stage, C_β acquires cationoid reactivity and is attacked by anionoid water (or an alcohol molecule) the mass of which greatly exceeds that of the chloridions. A small proportion of ethylene dichloride is always formed.

(*c*) Finally the complex loses a proton to a solvent molecule.

This mechanism serves to explain the formation of CH_2Cl·CH_2·O·CH_2·CH_2Cl when the concentration of the chlorohydrin rises.

The idea was criticised by W. A. Noyes, who preferred to postulate the formation of hypochlorous acid or an alkyl hypochlorite and its addition to ethylene. Subsequently, however, evidence accumulated from many directions which rendered untenable the hypothesis that hypochlorous acid or its esters are intermediates.

The rate-determining reaction is that between chlorine and ethylene; moreover hypochlorous acid is found to be far less reactive than chlorine. Again in certain similar reactions the hypochlorous acid type of view cannot be suitably adapted because the intermediate required is unknown and would probably be extremely unstable. To take one instance, bromine reacts with ethylene in the presence of aqueous sodium nitrate so as to form β-bromoethyl nitrate, CH_2Br·CH_2·ONO_2. The result conforms to the mechanism suggested but can hardly be due to formation of $BrNO_3$ (Terry and Eichelberger, *J. Amer. Chem. Soc.*, 1925, **47**, 1067; A. W. Francis, *ibid.*, p. 2340). Bartlett and Tarbell (*ibid.*, 1936, **58**, 466) made an elegant kinetic study of the addition of methyl hypobromite to stilbene, and reached the following conclusions.

" (1) The rate of bromination of stilbene in methyl alcohol solution is sharply diminished by bromide ions but not by hydrogen ions.

" (2) Therefore, although stilbene methoxy bromide is the principal product, methyl hypobromite is not responsible for its formation.

" (3) The kinetics of the reaction is consistent with a mechanism of reaction in two steps, in which molecular bromine is the active agent."

And here the lecturer wishes to take the opportunity to insist on the original form of his hypothesis and to deprecate the later versions which postulate a fully polarised ethylene $\overset{+}{C}H_2{-}\overset{-}{C}H_2$ and halogen cations, *e.g.*, $\overset{+}{Br}$. Similarly the second phase involves the neutral solvent molecule, *e.g.*, water, and not the hydroxyl ion as has sometimes been assumed. It is probable that the polarisation swings of ethylene in the resting or even the activated state indicated by $CH_2{=}\overset{\curvearrowright}{C}H_2$, represent only a small fraction of the full displacement of an electron pair. If it were otherwise the substance would be far more prone to polymerise than is found

to be the case, and it would also react with anionoid reagents. But once the electron donation from an ethylene molecule has commenced, strain is relieved, and the process can be continued. Hence the full displacement is assumed to occur only in the course of the reaction. Again the process is not one of interaction with halogen cations but with halogen molecules, because the concentration of the former, if they are present at all, must be extremely low and the kinetics would be inexplicable. Finally the concentration of hydroxyl ions in the strongly acid solution is certainly exiguous.

The Conjugated Systems.—(1) *Polyenoid.* In 1911 Hugo Kauffmann (" Die Valenz Lehre ", Enke, Stuttgart) developed a theory of partial and distributed valency which he applied with success to the problem of auxochromes and to the constitutions of benzene and the triphenylmethane dyes. He appears, however, to have regarded chemical affinity as a special kind of force and speaks of the valence fields becoming electric fields, if electrons are interposed. In other respects too, and particularly in the development, Kauffmann's views differed from those that the lecturer developed from 1916 (*J.*, 1916, **109**, 1032, 1041; 1917, **111**, 959; 1918, **113**, 643; *Mem. Manchester Phil. Soc.*, 1920, **64**, No. 4) and which were translated in 1922 into definite electronic symbols (Kermack and Robinson, *J.*, 1922, **121**, 427).

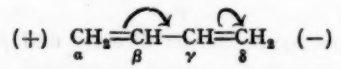
It was postulated that a valency bond could be subdivided, to an unknown but large extent, and it was further assumed that molecules are polarised by such partial division of the bonds. The polarised complexes enter into reactions. Thus taking four subdivisions of a bond, for convenience only, the activation of ethylene was represented as

With this polarised form the reaction, say addition of bromine, could be initiated and it was supposed to be completed in the course of the process by further division and rearrangement of the valencies. This view differed from that of Thiele in that the partial valencies were derived from the normal valencies and were not additional to them. The schemes for butadiene illustrate this contrast of which the most significant aspect is the assumption of polarisation:

Thiele. Robinson.

Here the signs on C^{β} and C^{γ} represented the polarity of the partial valencies from which the central partial bond was derived. It was an error to retain these signs after the part bond was formed, but the convention gave the right results in more complex systems.

Although these ideas were based from the commencement on the electronic theory of valency, use was made for some years of the partial polarised valency expressions. It was realised that the partial valencies labelled (−) represent available electrons, or part of an electron, and that those labelled (+) represent corresponding electron defect. Therefore the equivalent electronic symbol for polarised butadiene is:



This implies that a certain electron value, possibly quite a small fraction of one electron, becomes free on C^{δ} and that the resulting electron defect on C^{γ} is made up by the transfer of a corresponding electron fraction from the $C^{\alpha\beta}$ bond to $C^{\beta\gamma}$; and that this produces a corresponding electron defect on C^{α}. A very important feature of this representation is that, apart from the inevitable electron defect on one carbon atom, the number of quantised electrons in the configurations of the carbon atoms is unchanged. The mechanism of addition to this system will then be precisely analogous to that already discussed for ethylene. It will be noticed that the process transfers electron defect from C^{γ} to C^{α} but this event does not *always* occur. The left-hand arrow need not come into operation and, as experience shows, we may observe $\gamma\delta$ (or $\alpha\beta$) additions. It is obvious, and was clearly stated, that a double bond can transmit *any* effect of electron accession or recession and one or more double bonds can there-

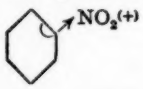
fore be interpolated in any system AB such that the quality of reactivity exhibited is due to a displacement of electrons from A to B, directly, or through an external circuit.

Much later Fuson (*Chem. Reviews*, **1935**, **16**, 1) called this the " Principle of Vinylogy ". It is a theoretical potentiality which is not always realised in practice. The effects may be greatly damped, and there are special exceptions such as R·Cl, R·CH=CH·Cl, the cause of which is apparent.

The polarised complexes of which butadiene is the type are called *polyenoid*. They include benzene and other aromatic hydrocarbons.

We are now in a position to consider why an electric field over the benzene nucleus should produce *op*-substitution or *m*-substitution according to its direction and intensity (Allan, Oxford, Robinson, and Smith, *J.*, **1926**, 409).

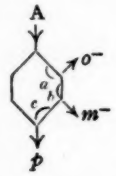
The reagent in nitration is cationoid; * it is looking for electrons. Therefore the first stage of the nitration of benzene could be represented as:



The second stage is the removal of the proton at the point attacked. That is also important but need not enter into the present discussion.

Now suppose we have a group (A) which promotes electron accession to the nucleus and a

general drift or repulsion of electrons as shown in the figure. Its effect will be a maximum at the carbon atom to which it is attached and less work will be needed to effect the polarisation (*a*) than (*b*) or (*c*):



Thus *o*-substitution can be expected. If the reagent approaches the *m*-position substitution may occur through the independent operation of (*b*) but it will be far less facile. But if the reagent approaches the *p*-position and enters into tentative union with it, the defect on the *m*-carbon can at once be made up by a conjugative process (*d*) which will be favoured by the same circumstances that helped (*a*):

Thus the push from (A) promotes *o*-substitution directly and *p*-substitution by conjugation. It is important to note that the process (*b*) cannot be assisted in a similar fashion, because in the expression

the number of electrons in the configuration of the *m*-carbon is increased.

We have seen that methyl is an (A) group; the percentage of *m*-nitration of toluene is 4 and the ratio of *o*- to *p*-nitration is about **3 : 2** (*o*-, 59%; *p*-, 37%).

* It is not certain that NO_2^+ is the sole nitrating agent; electrically neutral cationoid complexes are probably operative under appropriate conditions.

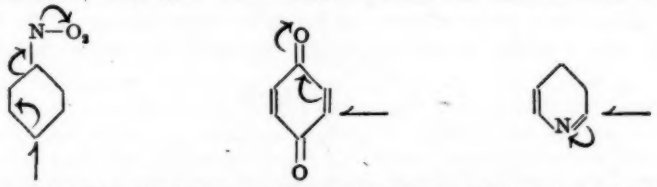
A group (B) which attracts electrons is equivalent so far as the field effect is concerned to an imaginary (A) group at the *p*-position:

Hence by the argument already given we anticipate *op*-substitution with respect to (A). That is, *m*-substitution with respect to (B), or displacement of that group by the substituent. The latter phenomenon is often encountered.

Naturally this use of the imaginary (A) group must not be pressed too far. The group (B) is real and by its positive electric field it renders all the nuclear electrons less available and reduces the ease and velocity of the substitution reaction.

(2) *Catio-enoid.* The cationoid reactivity of the carbon of a carbonyl group has been attributed to the electronic displacement $\rangle C{=}O$. This can be conjugated with a double bond and thereby the quality of reactivity of a carbonyl is transferred to a carbon of the ethenoid system $C{=}C{-}C{=}O$ (γ, α). It is another example of the $\alpha\gamma$ rule. Thus a cyanidion attacks the γ-carbon (usually denoted as β) in an unsaturated ketone. Consideration of these and similar cases led Lapworth (1920) to formulate his theory of alternate polarities expressed: $\overset{+}{C}{=}\overset{-}{C}{-}\overset{+}{C}{=}\overset{-}{O}$. In this way he merely indicated the polarities which the various atoms seemed to display at the moment of reaction. The device led to some useful and interesting results but it was certainly taken too literally, and Lapworth's clearly stated reservations were often overlooked by other workers. Later (1922) he adopted a view similar to that suggested by the lecturer, but this was presented in a very general form which was somewhat difficult to assimilate.

In the aromatic series, catio-enoid systems may lie outside the nucleus, partly in the nucleus, or wholly in the nucleus. They give rise to typical reactions with *anionoid* reagents:



Examples are the hydrolysis of nitrosodimethylaniline and 1-chloro-2 : 4-dinitrobenzene, the amination and hydroxylation of nitrobenzene, quinones, and pyridine, etc. etc.

(3) *Hetero-enoid.* H. Decker (Decker and Klauser, *Ber.*, 1904, **37**, 523; Decker, *Ber.*, 1905, **38**, 2893) suggested that tervalent nitrogen could be conjugated with a double bond, and employed the Thiele symbol: $C{=}C{-}\overset{\frown}{N}$:. The experimental basis of the divided addition concerned only the action of acids and therefore the mobile proton. The lecturer (*J.*, 1916, **109**, 1038) showed that alkyl groups could be used to mark the position of combination as in the examples:

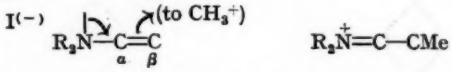
$$Me{\cdot}C(NEt_2){=}CH{\cdot}CO_2Et \xrightarrow{MeI} Me{\cdot}C(\overset{I}{\overbrace{NEt_2}}){=}CHMe{\cdot}CO_2Et \xrightarrow{H_2O} EtNH_2{\cdot}HI + Me{\cdot}CO{\cdot}CHMe{\cdot}CO_2Et$$

$$Me{\cdot}C(NMe_2){=}CMe{\cdot}CO_2Et + MeI \longrightarrow Me{\cdot}C(\overset{I}{\overbrace{NMe_2}}){=}CMe_2{\cdot}CO_2Et \xrightarrow{H_2O} Me{\cdot}CO{\cdot}CMe_2{\cdot}CO_2Et$$

This latter case excludes the hypothesis

$$\rangle C{=}CH{\cdot}CO_2Et + RI \longrightarrow \rangle C{=}CR{\cdot}CO_2Et + HI.$$

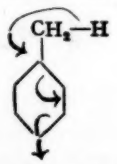
The basic nitrogen attached to the double bond has transferred, to unsaturated carbon, its own power of combining with a cationoid methyl group. The facts were established in the partial valency period and expressed in terms of that hypothesis. The electronic translation (1922) is much simpler and more convincing.



The unshared electrons (lone pair) of the nitrogen atom are used to increase the covalency with the nearest unsaturated carbon Cα. This must release electrons of the double bond to Cβ which can thus bind the methyl group. At the same time the nitrogen acquires a positive charge to balance the iodion, for it started with unshared electrons which became shared in the process.

It is quite clear that this system must be definitely anionoid or electron donating. For though olefins are anionoid the tervalent nitrogen is far more strongly so, and here the nitrogen atom endows the unsaturated group with something of its own quality. Furthermore this type of conjugation is possible if the nitrogen atom is replaced by any atom which carries unshared electrons, and the order of activation will be that of the proton-affinity (or basic strength) of the hetero-atom: the greater that affinity the more reactive will be the anionoid carbon. Thus $N^- > O^- > N > O > I > Cl$ to mention a few of the possibilities. The *C*-alkylation of the sodio-derivative of ethyl acetoacetate which is derived from the enolic form, is seen to be analogous to the *C*-alkylation of the β-aminocrotonic esters. The most important examples are in the aromatic series, *e.g.*, the phenoxide ion, the aromatic amines, phenols and their ethers, halogenobenzenes. All the characteristic nuclear reactions of phenols and amines, *e.g.*, bromination, nitration, condensation with carbonyl compounds, etc., are with cationoid reagents, and all occur exclusively in the *op*-position. The conjugations

provide a much more definite mechanism of activation than that previously considered, and they take precedence over other effects. It has been suggested by J. W. Baker and Nathan (*J.*, 1935, 1845) that a methyl group can release electrons in a somewhat similar fashion:

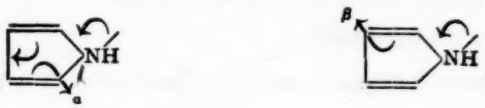


The relation of this suggestion to the use of unshared electrons in the systems under discussion is not yet clear.

The case of chlorobenzene is very interesting because its nitration, for example, is far less facile than that of benzene itself. This was to be expected, for chlorine is known to be an electron-attracting group as we have already seen:

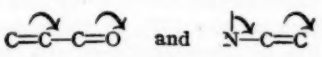
All the electrons of the nucleus are less available than they are in benzene. But even at this low level of reactivity the conjugative process determines where the donor electrons are to be found (see below, mesomerism).

Other important hetero-enoid systems are recognised in such substances as pyrrole, and account for the correspondence of its reaction types with those of phenol and dimethylaniline:



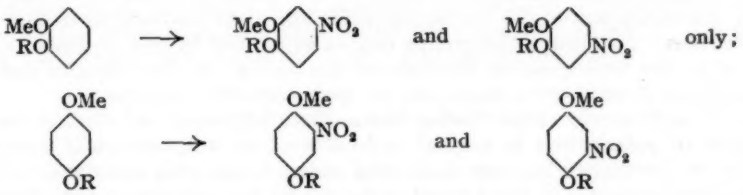
The α-positions are like the *p*-position in aniline, whereas the β-positions resemble the *o*-positions in aniline. They are all reactive as shown by the formation of tribromoaniline on the one hand and tetraiodopyrrole on the other.

The recognition of two kinds of conjugated changes of covalency with simultaneous increase or decrease of the unshared electrons of atoms such as oxygen or nitrogen as in

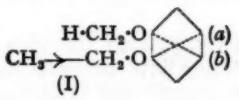


must be regarded as one of the milestones on the road we have travelled.

An Example of the Interaction of the Conjugated Polarisation and General Electric Effects.—A very important aspect of the lecturer's views was experimentally illustrated by a carefully selected case (three preceding papers were discussed by Allan, Oxford, Robinson, and Smith, *loc. cit.*; Lea and Robinson, *J.*, 1926, 411; Oxford and Robinson, *J.*, 1927, 2239; Fawcett and Robinson, *J.*, 1927, 2415; Clarke, Robinson, and Smith, *J.*, 1927, 2647; Smith, *J.*, 1931, 251). This was the mono-nitration of alkyl ethers of catechol and quinol (OMe, OR) which proceeds quantitatively. The proportions of the products can be determined accurately by thermal analysis.

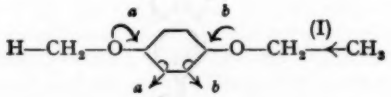


If we consider the case of the ethyl ether of guaiacol, there are two hetero-enoid systems directing *p*-substitutions as indicated by the dotted lines:



The oxygen of the methoxyl group directs the substituent to (*b*), that of the ethoxyl group to (*a*). In the ethoxyl group a hydrogen of the methoxyl group is replaced by methyl, and this, as we know from strengths of acids and bases and from the dipole moment of toluene, will repel electrons relative to the effect of hydrogen. Hence the system terminating in (*a*) should be reinforced and the directive power of ethoxyl should exceed that of methoxyl; which is actually found to be the case. Taking MeO, 100 we find EtO, 135. But on increasing the size of R in OR, the directive power rises to a maximum and then falls: Pr$^{\beta}$O, 150; Pr$^{\alpha}$O, 128; *n*-BuO, 123.

The effect (I) (inductive or general) is evidently also exerted on the oxygen of the methoxyl as the stereochemical conditions suggest that it should be, and the distributed direct effect partly neutralises that exerted through the chain. But in the quinol series this is no longer true:



The push of the methyl now assists (*b*) and actually opposes (*a*). Hence the directive power of EtO (164) is higher than that found in the catechol series. And with larger groups it continues to increase (Pr$^{\alpha}$O, 180; *n*-BuO, 186; *n*-$C_{16}H_{33}O$, 212).

An electron-attracting group is *p*-nitrophenyl, and here the circumstances are reversed. In the catechol series $NO_2 \cdot C_6H_4 \cdot CH_2O$, 67, and in the quinol series, 38. The distributed pull on the electrons of the oxygen atoms in the former case results in a higher directive power than the pull in the latter case acting on the oxygen of the nitrobenzyloxy-group alone. One apparent exception was noted in the benzyloxy-group (113 in the catechol series, 107 in the quinol series), but the differences are small and the value in the catechol series is suspect. In the course of the Faraday Society discussion in 1923, it was stated that the polarity theories

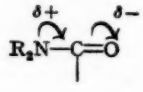
explained everything and predicted nothing. The lecturer thereupon made a prediction as follows :

(1) That the *para*-chlorobenzyloxy-group would have a greater orienting power than *meta*, and

(2) that the *para*-nitrobenzyloxy-group would have a weaker orienting power than the *meta*.

In 1927 the first prediction was justified (*p*-, 82; *m*-, 69), but the *m*- and *p*-nitrobenzyloxy-groups had nearly the same directive powers (67), in the catechol series. The anticipated effect was, however, noted with the nitrobenzamido-groups in the acylated *p*-phenetidine series (EtO, 100; *p*-, 190; *m*-, 226).

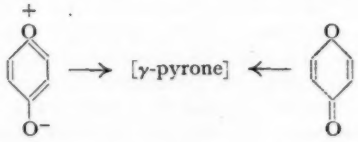
The Neutralised Systems.—If a strongly cationoid group is attached to a strongly anionoid group, *e.g.*, N to CO, electron transfer occurs in the molecule under all conditions :



The result is in this case to diminish the basic character of N and the cationoid character of C of CO and to produce a definite dipole evinced by the physical character of the amides. In a similar way the characters of the carboxylic acids and their derivatives receive a very convincing explanation. As always the groups can be separated by one or more double bonds, and the extent of the neutralisation depends on the affinity of the nitrogen and oxygen, or what corresponds to them in other examples, for their respective charges.

The Condition of Molecules in the Resting State.—Both Lapworth and the lecturer postulated a certain degree of polarisation in normal molecules of an unsymmetrical nature, but paid little attention to the matter because their chief concern was with reactions. The existence of electromeric displacements in the normal molecules of the conjugated complexes was, however, always mentioned in lectures in various centres on these topics and in University teaching from 1922. Indeed, the views expressed in regard to neutralised systems such as the amides, and the references to their physical and chemical properties, were meaningless without this assumption.

In the case of certain classes of compounds the idea was emphasised, and the pyrones, for example, were recognised as intermediate between the fully polarised hydroxypyrylium betaine and the usual neutral formula (Armit and Robinson, *J.*, 1925, **127**, 1604) :



Arndt, Scholz, and Nachtwey (*Ber.*, 1924, **57**, 1903) put forward a similar view of " Zwischenstufe " based on the properties of a series of thiopyrones. They did not interpret their hypothesis in terms of electronic displacements.

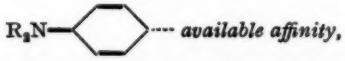
Another way of representing the matter is to say that the pyrones are normally

and it will be noticed that this is merely a neutralised system of ester type, $-O-CO-$, in which a double bond is interpolated in two places. There is, however, the additional circumstance that the pyrylium nucleus is aromatic, and that was considered to be an important factor in producing a closer approximation to the pyrylium betaine than would otherwise be the case.

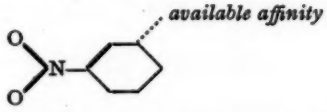
Ingold and Ingold (*J.*, 1926, 1310) introduced the convenient term " mesomerism " for this electromeric effect in normal molecules, and an outstanding contribution on the experimental side was made by L. E. Sutton. Using the method of measurement of dipole moments he was able to recognise the mesomerism of many aromatic compounds containing hetero-

enoid and catio-enoid systems as well as those in which both are present and may be partly neutralised. The direction of the mesomeric displacement was not necessarily in the same sense as the dipole. Thus the dipole in chlorobenzene was in the direction Cl← as the theory of the general effect demands. A small counteracting mesomeric effect Cl→ was detected by comparison of the moment of chlorobenzene with that of *tert.*-butyl chloride (*Proc. Roy. Soc.*, **1931**, **133**, 668). This work was a remarkable physical confirmation of the validity of the hypotheses which have briefly been expounded, for it was found that all *op*-directive groups examined increased the density of electrons in the aromatic nucleus and all *m*-directive groups decreased it. Methods for determining the occurrence and extent of mesomerism have been developed by Pauling and others, but they belong to the modern period. The device of writing down the possible structures and estimating the contribution which each makes to the actual condition of the molecule is a calculus and not a theory of structure, though it has often been misunderstood as such.

Conclusion.—Many important tributaries have been omitted from this account and the river has not been followed to the sea. Thus the work of Claus, Werner, and Flürscheim had a most important influence on the thoughts of chemists. Flürscheim's development of the theory of alternating and variable affinity was especially valuable. It gave the results now regarded as correct in many cases, as in the hetero-enoid systems:



but failed to meet our requirements in the catio-enoid systems:



The speculations of Vorländer and Fry likewise contained useful detailed suggestions but were eventually seen to be out of the direct line of progress. The lecturer has perforce had to omit all reference to the stereochemical aspects, such as the Mills–Nixon effect, to W. Baker's applications of chelation, to tautomerism, dissociating systems, and molecular rearrangement, as well as to many other topics of great interest. In particular he has not mentioned the neutral free radicals and atoms, which can be anionoid, *or* cationoid, *or* homopolar.

It seems peculiarly appropriate that a Faraday Lecture should deal with molecular electrical phenomena, although they are of a very simple kind, in relation to properties of the derivatives of benzene, a substance which Faraday discovered. We owe to him the first studies of dielectrics and as a twig from this tree we take the measurement of dipole moments. Above all he was a great electrochemist and was convinced that electricity and chemical affinity could be identified. His Laws of Electrolysis, considered from the point of view of atoms and ions, bear much the same relation to the atomic theory of electricity that the Law of Multiple Proportions bears to the atomic theory of the elements.

In the Faraday Lecture of 1881, Helmholtz said: " Now the most startling result of Faraday's Law is perhaps this. If we accept the hypothesis that the elementary substances are composed of atoms, we cannot avoid concluding that electricity also, positive as well as negative, is divided into definite elementary portions which behave like atoms of electricity ".

The logic is inescapable and yet we must admire the acumen and courage of the remark.

Without forgetting the work of Volta, Davy, and Berzelius, and of many other real pioneers in the middle and later periods, we are right to honour the memory of Michael Faraday, the most illustrious of the founders of a science of electrochemistry.

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